Overview of CDER Experience with Nanotechnology-related Drugs

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Associate Director for Research Policy and Implementation (OPS/CDER/FDA)

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 9, 2012

Outline of Session on Nanotechnology

	Topic	FDA Speaker
1	Introduction and Overview of CDER Activities in Nanotechnology	Nakissa Sadrieh
2	Overview of CDER Nanotechnology Risk Assessment Working Group	Elaine Morefield
3	Overview of CDER Research Relevant to the Review of Nanotechnology-related Drugs	Katherine Tyner

Overview

- Overview of Agency actions related to nanotechnology

- Preliminary results from analysis of CDER nanotechnology database

Nanotechnology Activities in FDA Centers

- Guidance development
- Workshops/public meetings
- Core research facilities (Arkansas and White Oak)
- Training offered to FDA staff by the Agency

Agency-level Activities

- There is no “official” definition of “nanotechnology” at FDA.
- FDA draft guidance document (June 2011): “Considering whether an FDA-regulated product involves the application of nanotechnology” identifies 2 criteria for assessing the use of nanotechnology in FDA-regulated products:

1. Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or
2. Whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer.

CDER Activities: OTC Drugs

- In addition to reviewing and approving INDs and NDAs involving nanotechnology, FDA is currently evaluating the safety of nanomaterials in over-the-counter (OTC) sunscreen drug products.
- Most OTC drugs may be marketed without prior review and approval by FDA if they comply with a regulation called an OTC monograph for the applicable therapeutic category. FDA is examining the safety of titanium dioxide and zinc oxide nanomaterials for sunscreen use as part of an ongoing regulatory proceeding to establish a final monograph for OTC sunscreen drug products.
- FDA has issued calls for data and information relevant to the safety of zinc oxide and titanium dioxide nanomaterials in OTC sunscreen drug products. FDA will determine the final monograph conditions for sunscreens after considering all data submissions together with the results of FDA's research and other available safety and efficacy data. Once a final monograph is in effect, any sunscreen that does not meet the conditions of the monograph will require an approved NDA or ANDA in order to be marketed.

CDER Activities: Sunscreens

- Agency response to a Citizen Petition ("nanotechnology" page on FDA website: www.fda.gov).
- Center has undertaken focused regulatory research to better understand whether sunscreens contain nanomaterials, and whether such nanoparticles might penetrate healthy skin.
- Ultimate regulatory treatment of sunscreens will be addressed through rule making process, but the Agency has not seen evidence that would compel it to believe that any harm can come from the use of sunscreens.

CDER Activities: New Drugs

- Building database of submitted applications that contain nanotechnology-related materials, according to CDER MAPP (“Reporting format for nanotechnology-related information in CMC reviews”).
- Conducting an in-depth risk assessment to evaluate products containing nanotechnology-related materials.
- Ongoing research projects

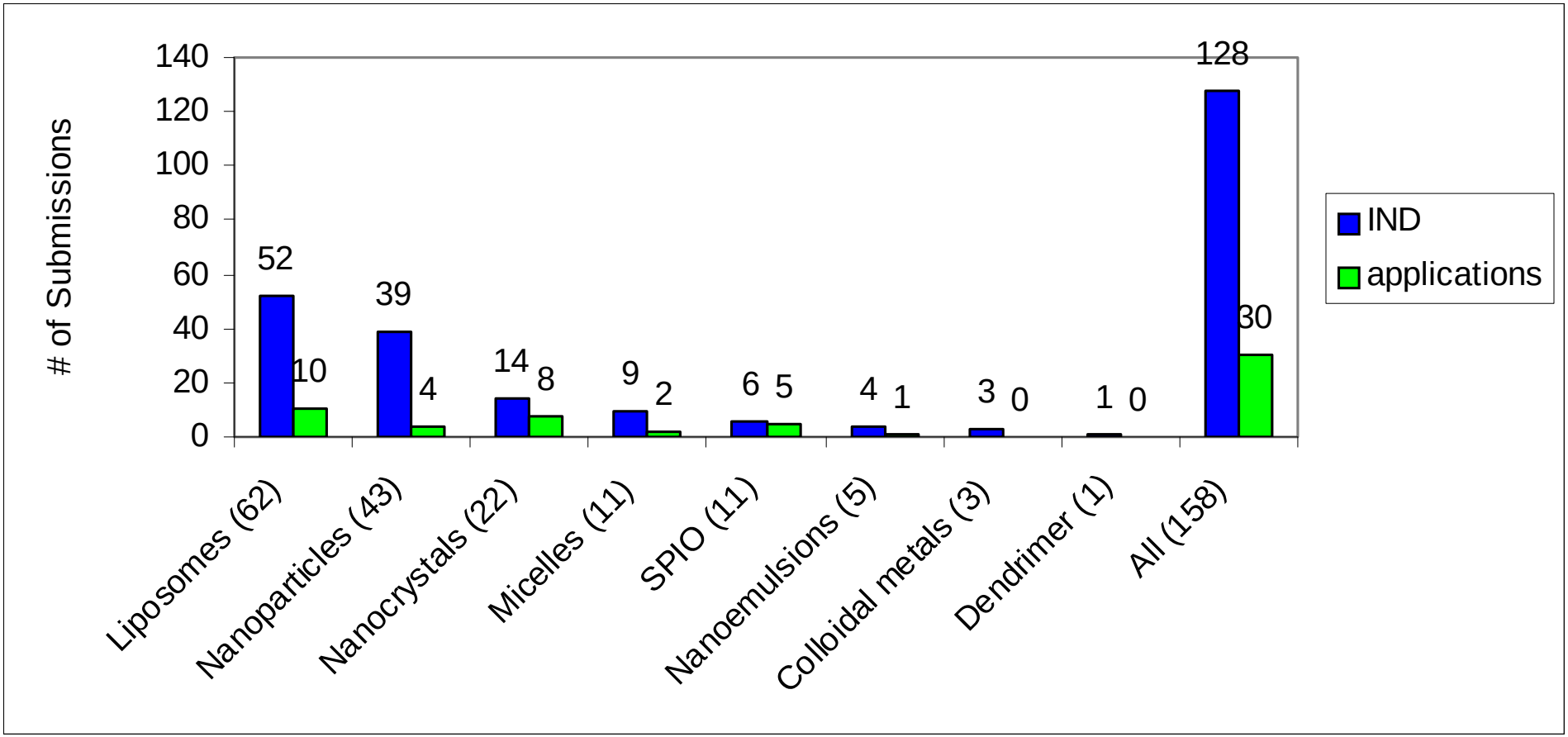
CDER Manual of Policies and Procedures for Drugs Containing Nanomaterials

- CDER MAPP: “Reporting format for nanotechnology-related information in CMC reviews” (June 2010)
- **Purpose of the MAPP:**
  - To collect in CDER CMC reviews, data submitted on nanotechnology-related information.
- **Criteria used for data collection:**
  - If the particle size of the product is reported in the submission as being under 1000 nm, then the CMC review should contain a table included in the MAPP.

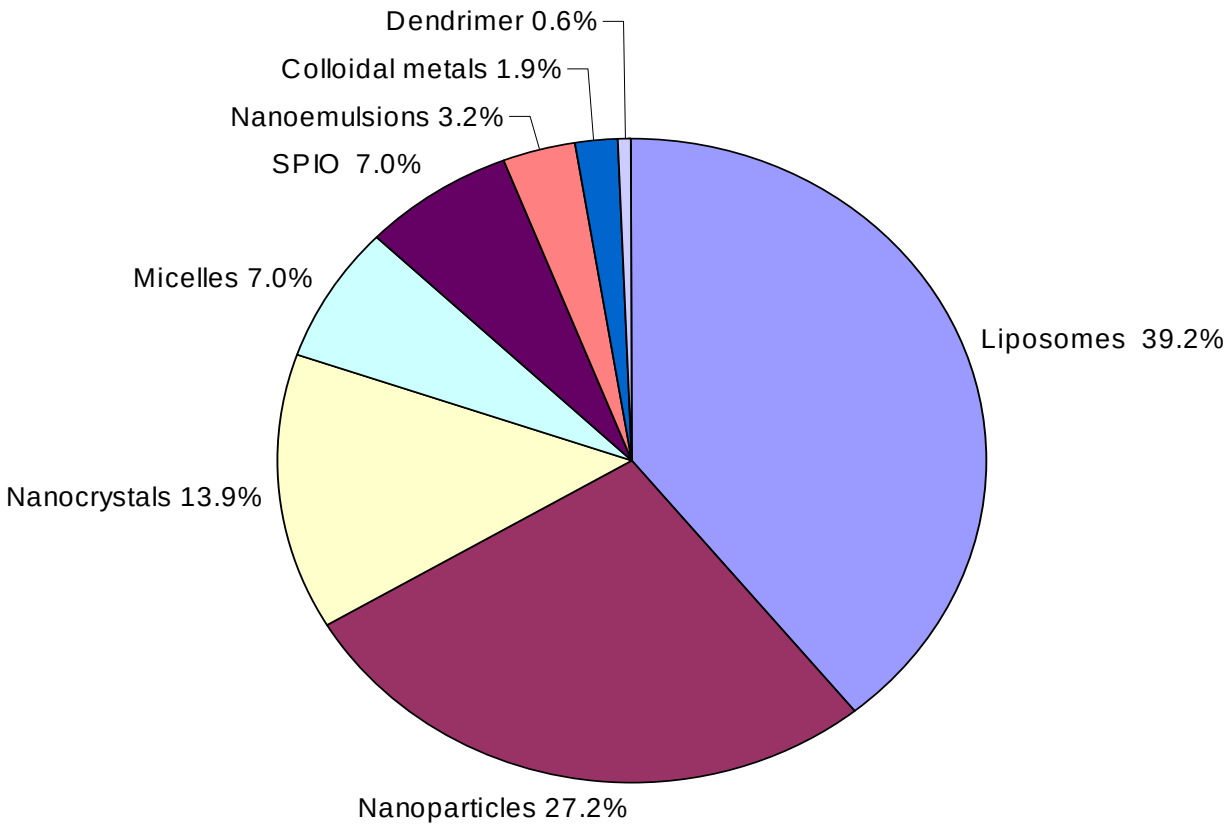
Evaluation of CDER Nanotechnology Database

- Drugs that use nanotechnology include:
  - New molecular entities formulated with components in the nanoscale.
  - Reformulations of already approved products:
    - a decrease in the particle size may change some aspect of the drug (such as targeted drug delivery, pharmacokinetic profile, a more convenient dosage form thus better patient compliance).
- Typical platforms include, but are not limited to:
  - Liposomes, nanocrystals, nanoemulsions, dendrimers, metal oxides (superparamagnetic iron oxide, titanium dioxide, zinc oxide), gold and silver nanoparticles.

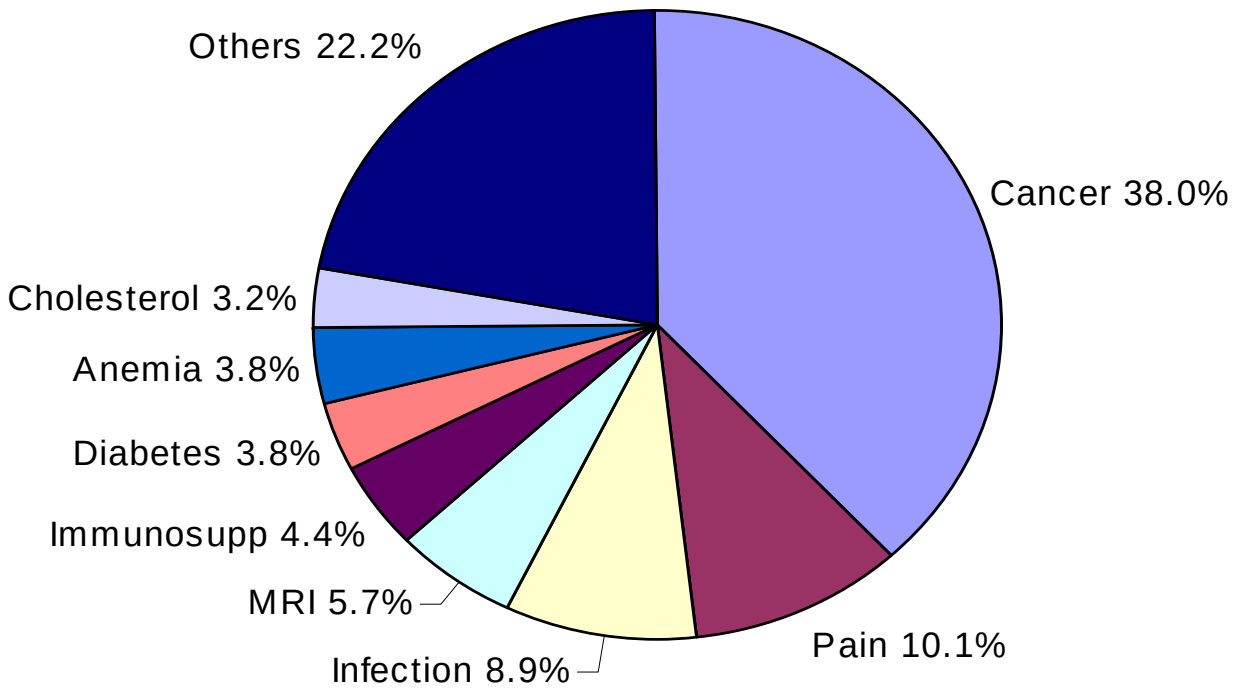
Nanotechnology-related Submissions



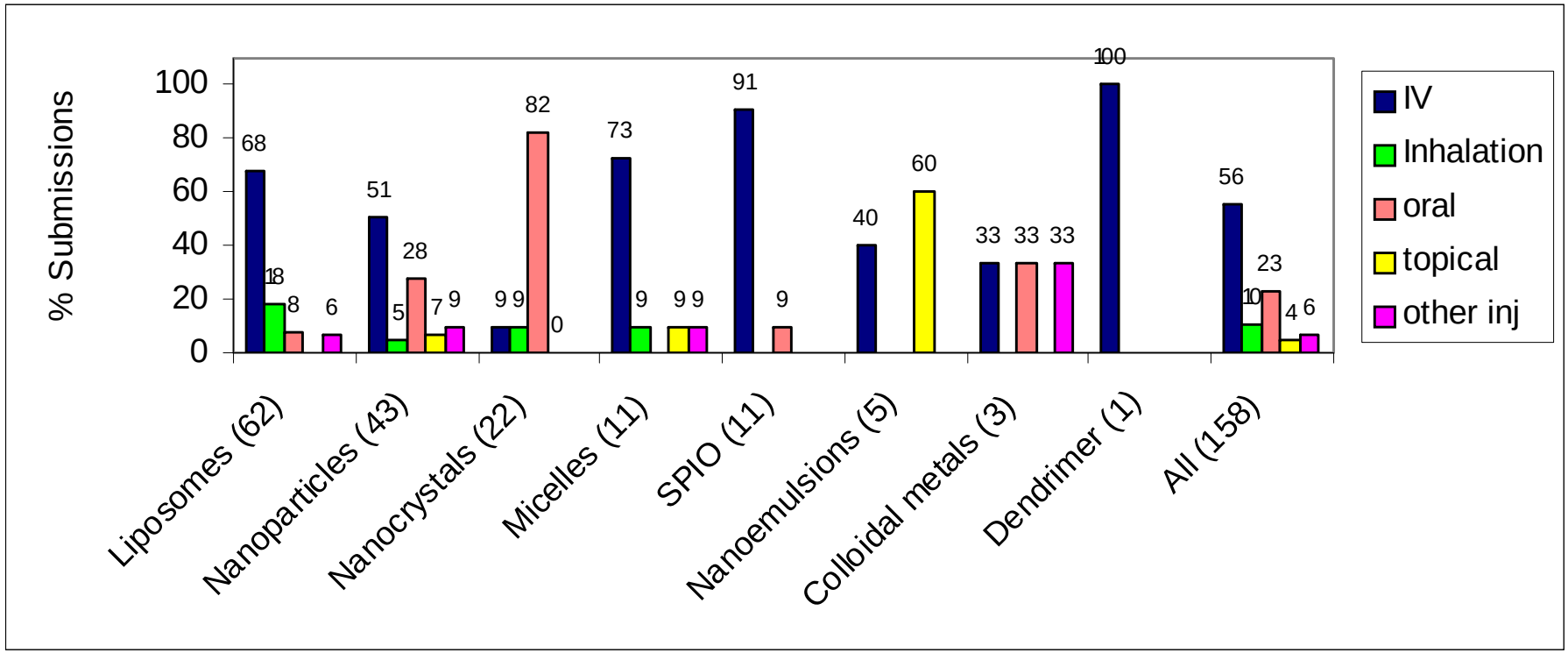
Nanotechnology-related Platforms



Indications



Routes of Administration



Characterization

- Many parameters may require characterization.
- But size specification of nanoparticles in bulk material and formulated drug product are important in understanding a drug's PK and PD profile.
- Size can be reported differently (mean or distribution).
- Different size measurement methodologies can have varying degrees of limitations.

Multiple Parameters…. Multiple Techniques

PROPERTIES[a]	COMMON TECHNIQUES[b,c]
MORPHOLOGY	
Size (primary particle)	TEM, SEM, AFM, XRD
Size (primary/aggregate/agglomerate)[d]	TEM, SEM, AFM, DLS, FFF, AUC, CHDF, XDC, HPLC, DMA(1)
Size distribution	TEM, SEM, AFM, DLS, AUC, FFF, HPLC, SMA
Molecular weight	SLS, AUC, GPC
Structure/Shape	TEM, SEM, AFM, NMR
Stability (3D structure)	DLS, AUC, FFF, SEM, TEM
SURFACE	
Surface area	BET
Surface charge	SPM, GE, Titration methods
Zeta potential	LDE, ESA, PALS
Surface coating composition	SPM, XPS, MS, RS, FTIR, NMR
Surface coating coverage	AFM, AUC, TGA
Surface reactivity	Varies with nanomaterial
Surface-core interaction	SPM, RS, ITC, AUC, GE
Topology	SEM, SPM, MS
CHEMICAL	
Chemical composition (core, surface)	XPS, MS, AAS, ICP-MS, RS, FTIR, NMR
Purity	ICP-MS, AAS, AUC, HPLC, DSC
Stability (chemical)	MS, HPLC, RS, FTIR
Solubility (chemical)	Varies with nanomaterial
Structure (chemical)	NMR, XRD
Crystallinity	XRD, DSC
Catalytic activity	Varies with nanomaterial
OTHER	
Drug loading	MS, HPLC, UV-Vis, varies with nanomaterial
Drug potency/functionality	Varies with nanomaterial
In vitro release (detection)	UV-Vis, MS, HPLC, varies with nanomaterial
Deformability	AFM, DMA(2)

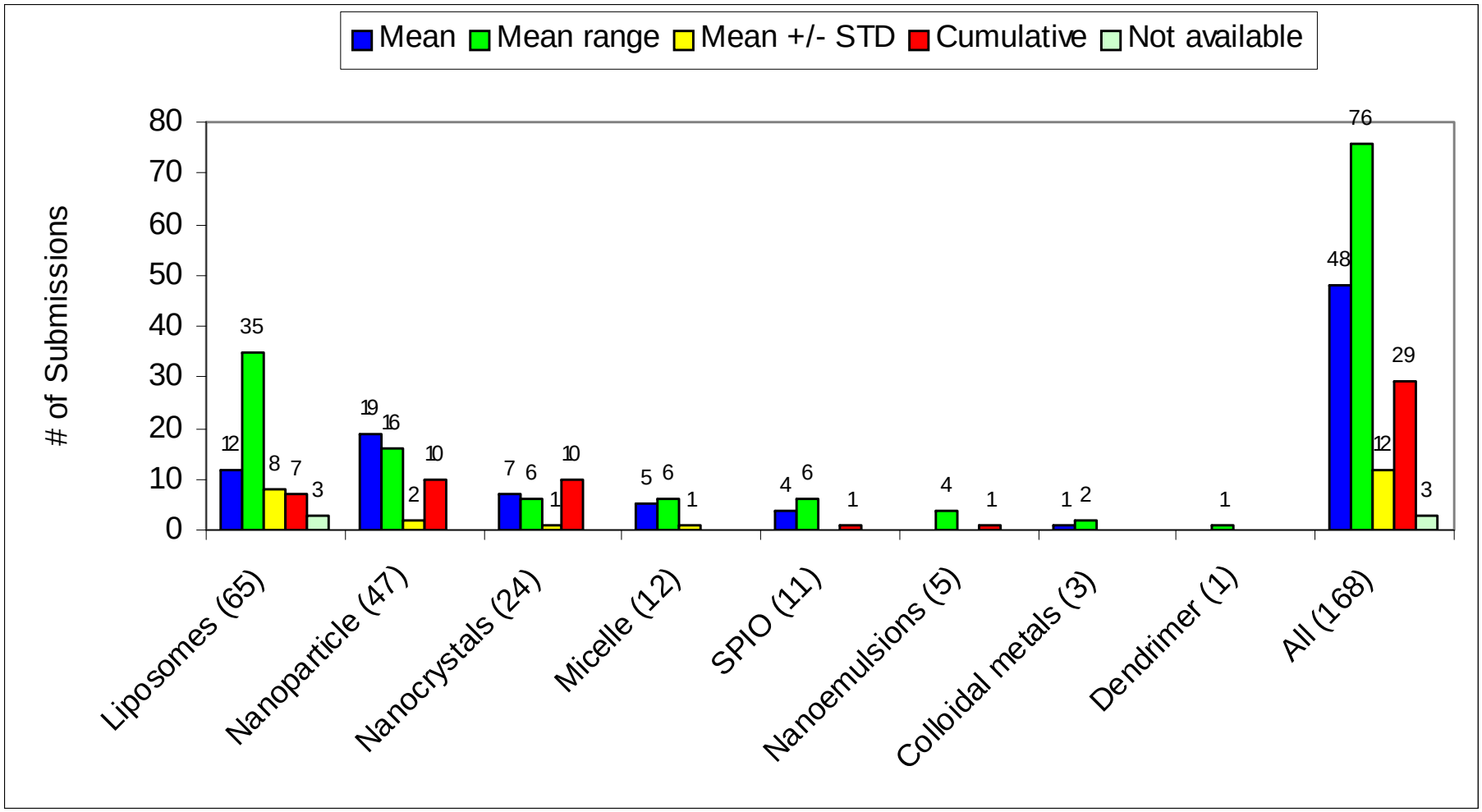
[a] *The property list is not definitive. Other properties may be reported.*

[b] *Only common techniques are listed. Other techniques may be valid. The choice of techniques should be justified.*

[c] *An abbreviation list and references are provided on the following page.*

[d] *These techniques will measure the average particle size, but can not necessarily distinguish between primary particles, aggregates, and agglomerates.*

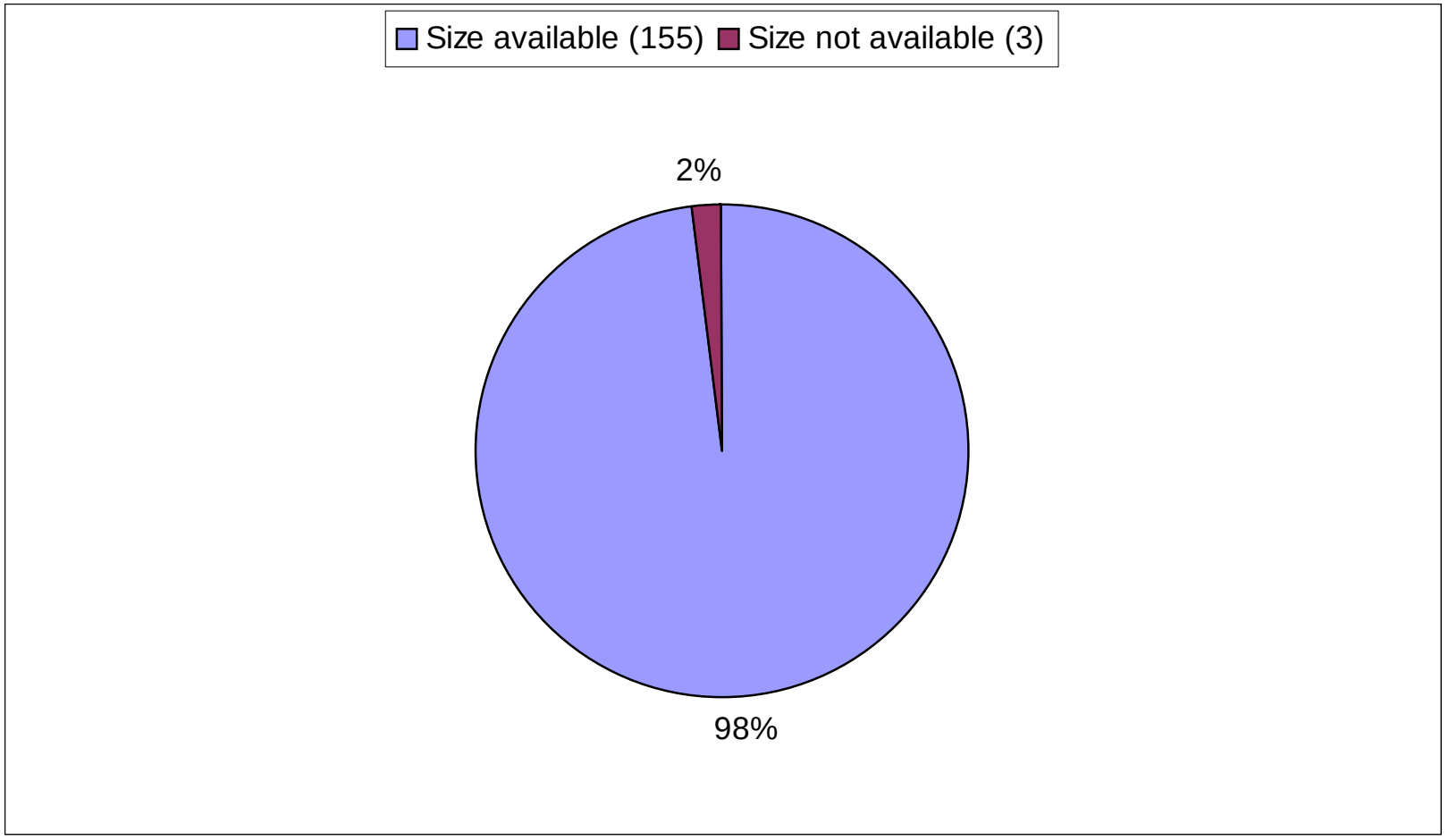
Particle Size Formats Reported in CDER Submissions



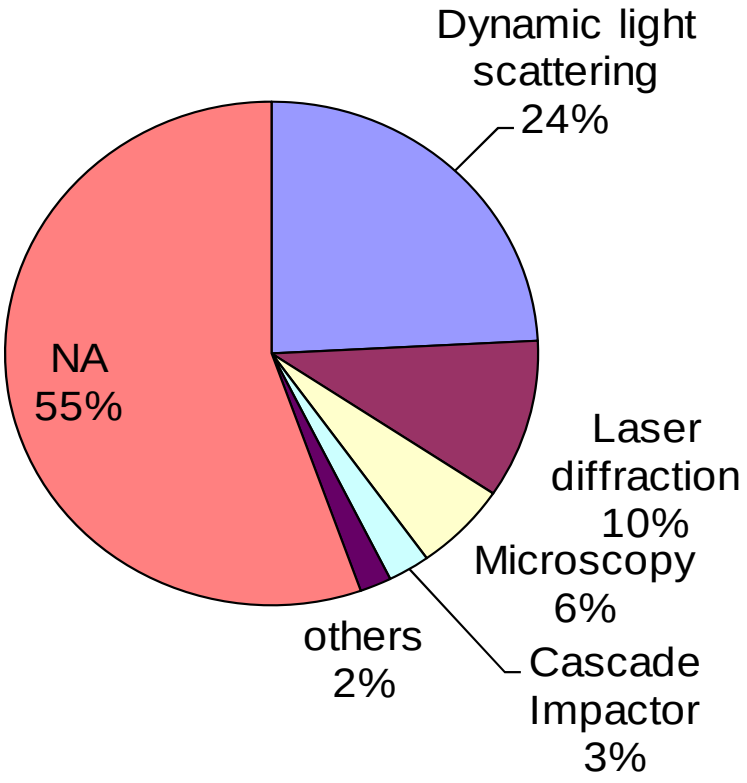
Assumptions Used In Analysis Of CDER Database

- Our analysis considered only one value for the mean, assuming that all measures of mean values were equivalent:
  - Mean, mean range, mean+/-SD, median
- Our analysis did not consider that different methods used to assess mean values (such as DLS, TEM, FFF, etc…) would introduce different degrees of variability, because of fundamental differences in the methods.
- Our analysis did not take into account inherent differences in formulations (e.g. suspensions versus powder) that would be impacted by the particle size measurement methodologies.

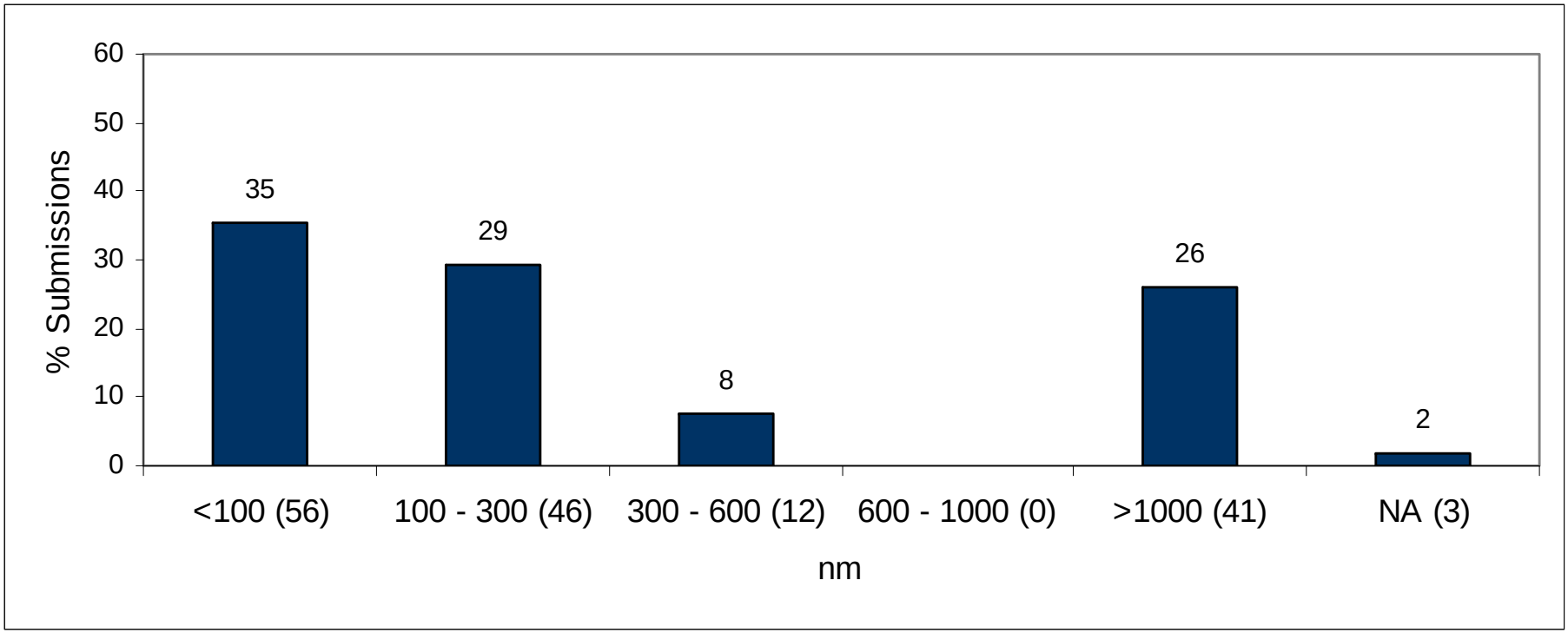
Percentage of Submissions With Some Form of "Mean Particle Size" Information



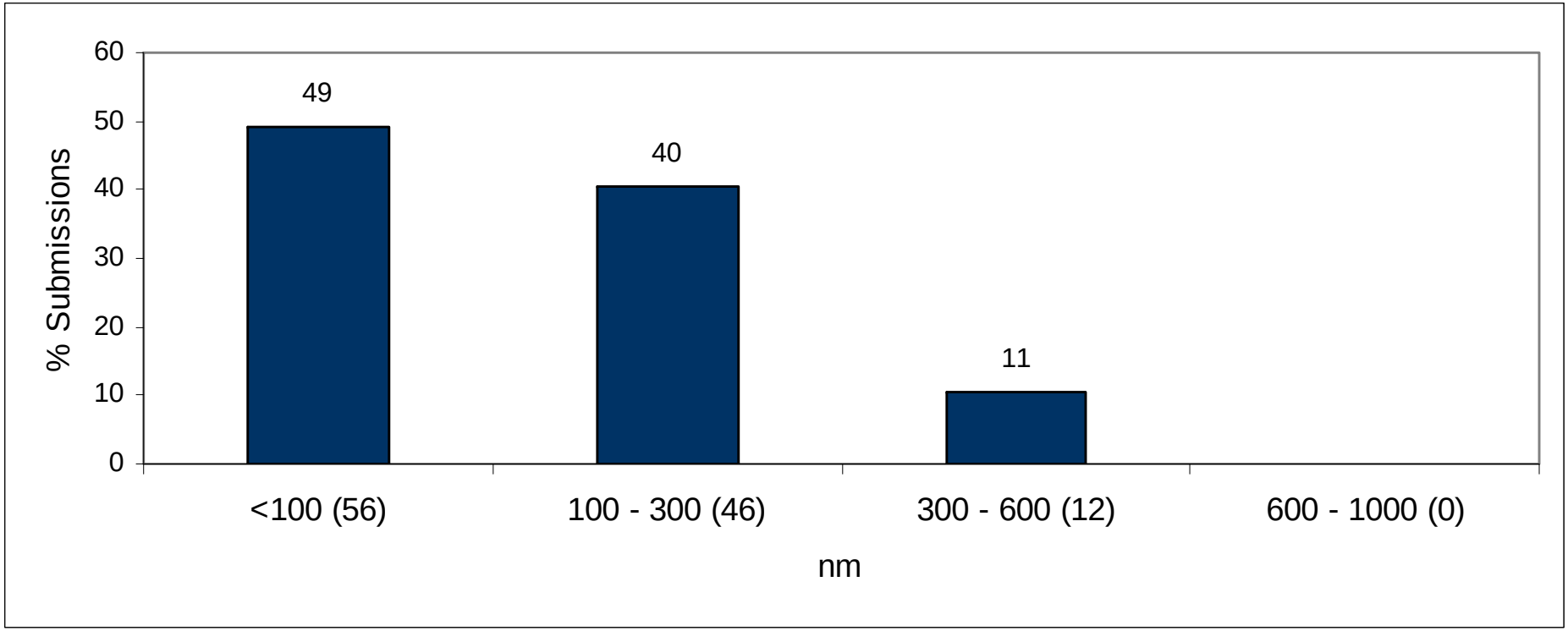
Particle Size Methodologies Used in Nanotechnology-Related Submissions



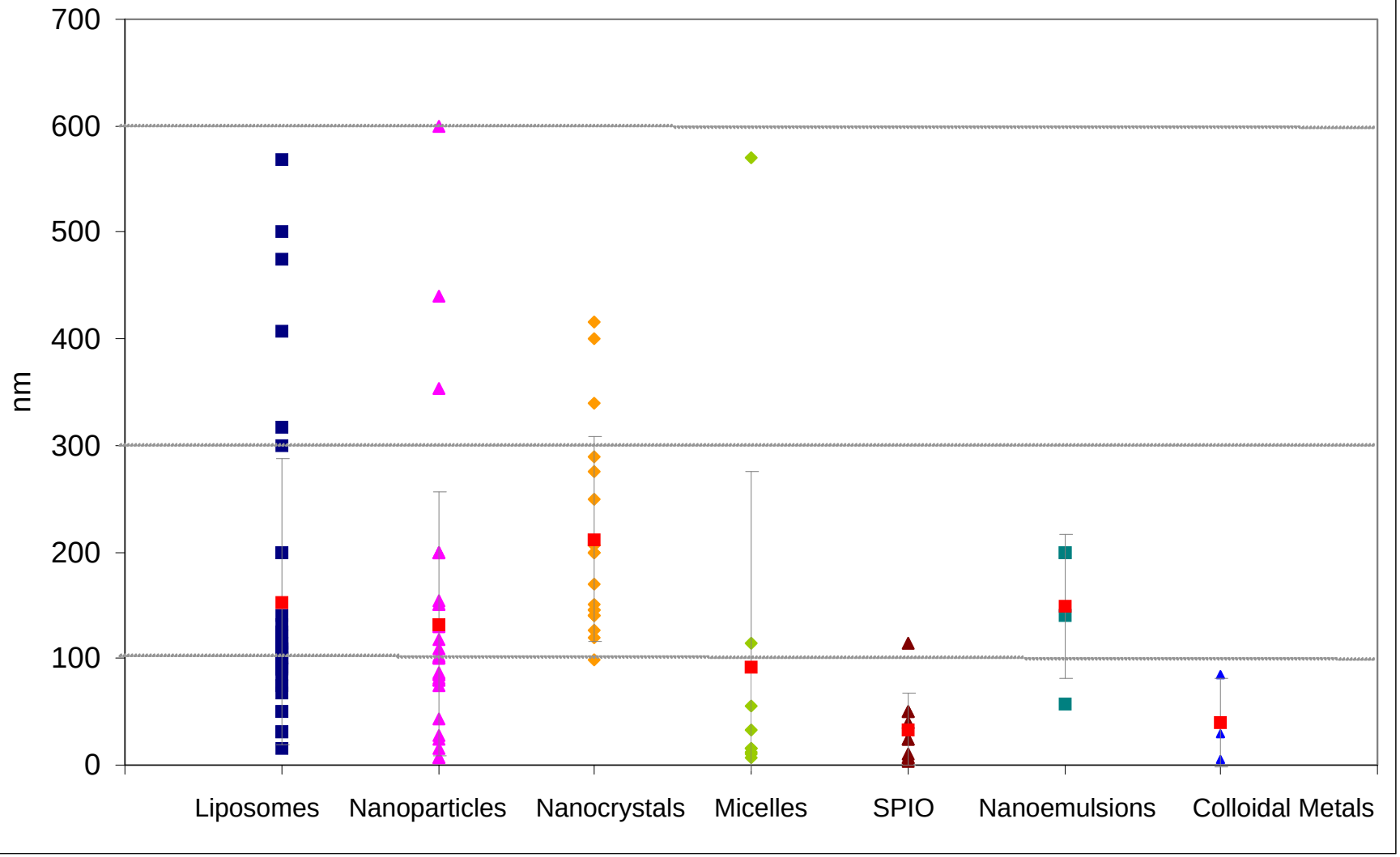
Reported "Mean" Particle Size For All Nanotechnology-related Submissions



Reported "Mean" Particle Size For Nanotechnology-related Submissions Under 1000 nm



Distribution of "Mean" Particle Size in CDER Database



Examples of Biological Responses Subject To Size Limitations

Biological responses	Size limits	Comments
Glomerular filtration	5-10 nm	Physiologic upper limit by renal clearance
Nanoparticles transport through liver sinusoid	300 nm	Liver fenestrae act as a sieve allowing only those particles smaller than the fenestrae to reach the liver cells. Size distribution of sinusoidal fenestrae among different species; 75 - 300 nm in rats, 45 - 255 nm in rabbits, 55 - 320 nm in mice and 50 - 300 in humans. Particle shapes and rigidity may further affect the size limit, for example, liposome sizes of up to 400 nm were able to cross the liver fenestrae.
Enhanced permeability and retention (EPR)	300-600 nm	EPR effects and neovasculature pore size may vary depending on the species, tumor implantation sites and tumor types. Nanoscale particles up to 300 nm in diameter extravasate through leaky tumor vasculature and selectively accumulate in tumor tissue via EPR effect. In study involving liposomes, sizes up to 600 nm in diameter were able to permeate through the tissues.
Reticuloendothelial system (RES) uptake	300 nm (surface modified particles with extended residence time	Nanoparticles are cleared by size dependent phagocytosis by the cells in reticuloendothelial system. Extended blood residence time of nanoparticles up to 200 – 300 nm.

Summary

- CDER has done a preliminary analysis of nanotechnology-related drugs submitted for review.
- CDER is continuing to learn from the data and the science.
- There are gaps in the data being analyzed, because submissions do not contain consistent data.
- CDER must continue to collect complete and consistent data, in order to better understand the issues involved.

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Questions For Advisory Committee

1. To assist data collection and analysis for CDER's database, please provide suggestions as to what are the appropriate characteristics or attributes to be considered to classify materials/products as nanotechnology related.
2. Please recommend any additional risk assessment elements to consider in refining CDER's approach to risk assessment/management.
3. Please suggest additional areas of research that CDER can focus on in order to determine the effects of nanotechnology-related materials used in drug products.

Results of CDER's Risk Management Exercise for Products Using Nanotechnology

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
August 9, 2012

Elaine Morefield, Ph.D.
Deputy Office Director for Review and Administration,
Office of New Drug Quality Assessment (ONDQA), OPS, CDER, FDA

Outline

- Background
- Introduction to the Nano Risk Assessment Working Group
  - Membership
  - Goals
- Risk Management Methodology: Nanomaterial API by Route of Administration and Excipients
  - Ishikawa Diagrams
  - Gap Analysis
- Risk Management Results
- Conclusions
- Next Steps

Working Group Roster

The team has membership from experts in various disciplines across CDER:

- Pharmacology/Toxicology
- Chemistry
- Biopharmaceutics
- Clinical Pharmacology
- Clinical
- Research

Working Group Goals

- *Technical*
  - To identify potential risks to safety, quality and efficacy resulting from the use of nanomaterials in drug products
- *Regulatory*
  - To identify areas for improvements based on identified risks and gap analysis

Systematic Approach

1. Ishikawa Diagram

- Tool used to identify the potential risk factors and map them by category
- These are factors that may lead to an effect on safety, quality and/or efficacy, if drug product component is a nanomaterial

2. Gap Analysis

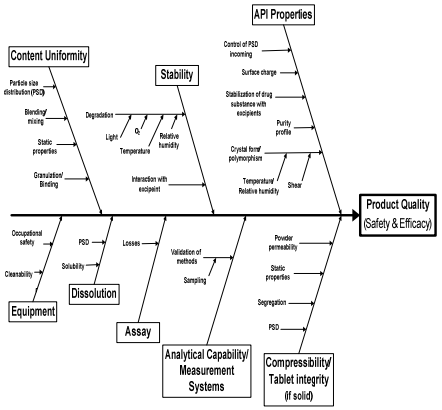
- Identify any areas for improvement in our current approaches (e.g., policy, review procedure, or data requirements)
- Document whether current approaches can evaluate the potential risk or whether additional work is necessary
- Develop recommendations

Identification of Potential Risk Factors to Safety, Quality & Efficacy (SQE) from Nanomaterial API

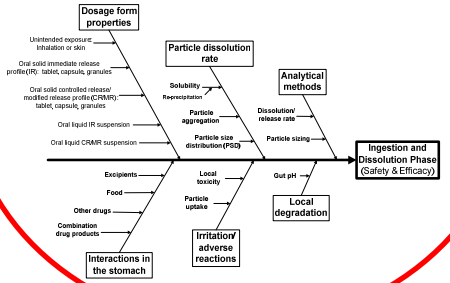
Oral Route of Administration

Product manufacture → Ingestion and dissolution → Absorption and distribution → Elimination

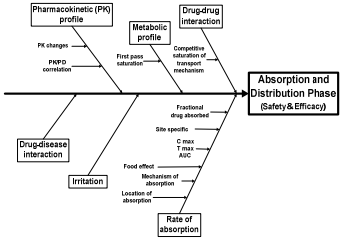
O1: Oral Administration, Potential Effects on Safety and Efficacy of Nanomaterial API at the Product Manufacture Phase



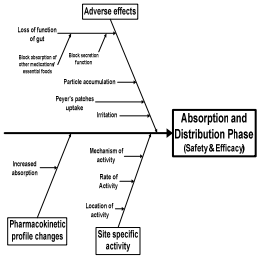
O2: Oral Administration, Potential Effects on Safety and Efficacy of Nanomaterial API at the Ingestion and Dissolution Phase



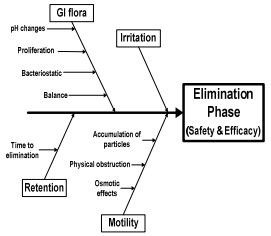
O3: Oral Administration, Potential Effects on Safety and Efficacy of Nanomaterial API at the Absorption and Distribution Phase for Particles Intended for Absorption



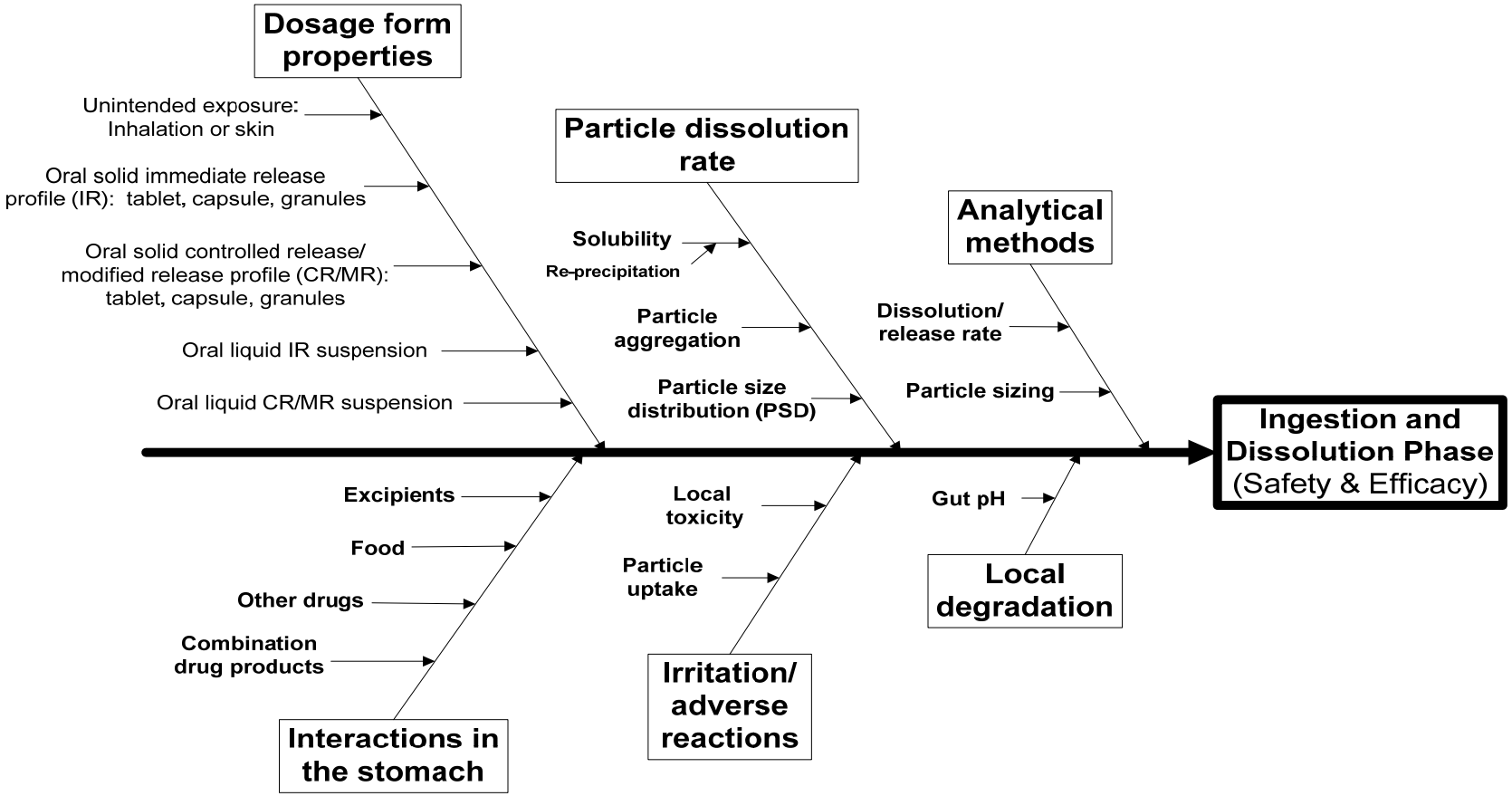
O4: Oral Administration, Potential Effects on Safety and Efficacy of Nanomaterial API at the Absorption and Distribution Phase for Particles Not Intended for Absorption



O5: Oral Administration, Potential Effects on Safety and Efficacy of Nanomaterial API at the Elimination Phase for Particles Not Intended for Absorption



O2: Oral Administration, Potential Effects on Safety and Efficacy of Nanomaterial API at the Ingestion and Dissolution Phase

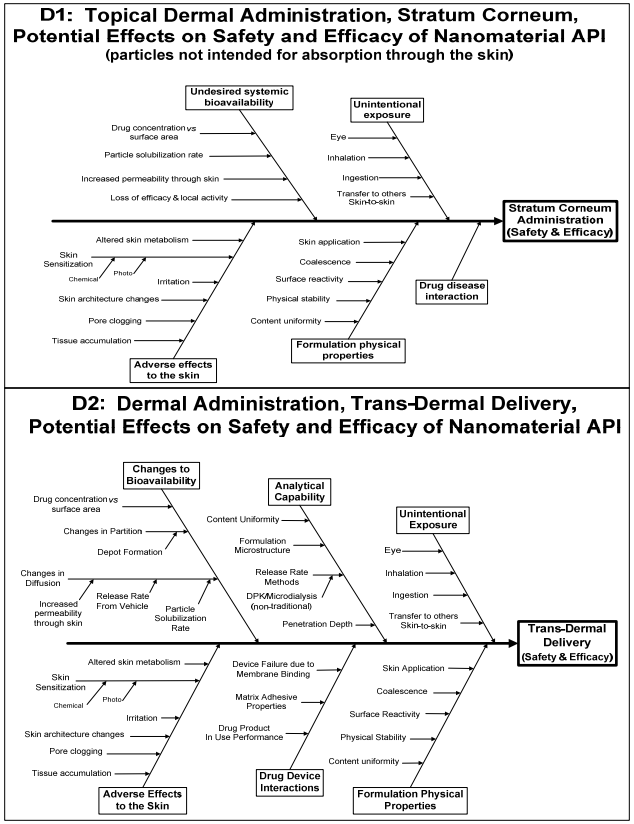


Identification of Potential Risk Factors to SQE from Nanomaterial API

Dermal Route of Administration

Dermal Application

- Locally active on the skin, particle not intended for absorption (D1)
- Transdermal delivery, particle intended for absorption (D2)

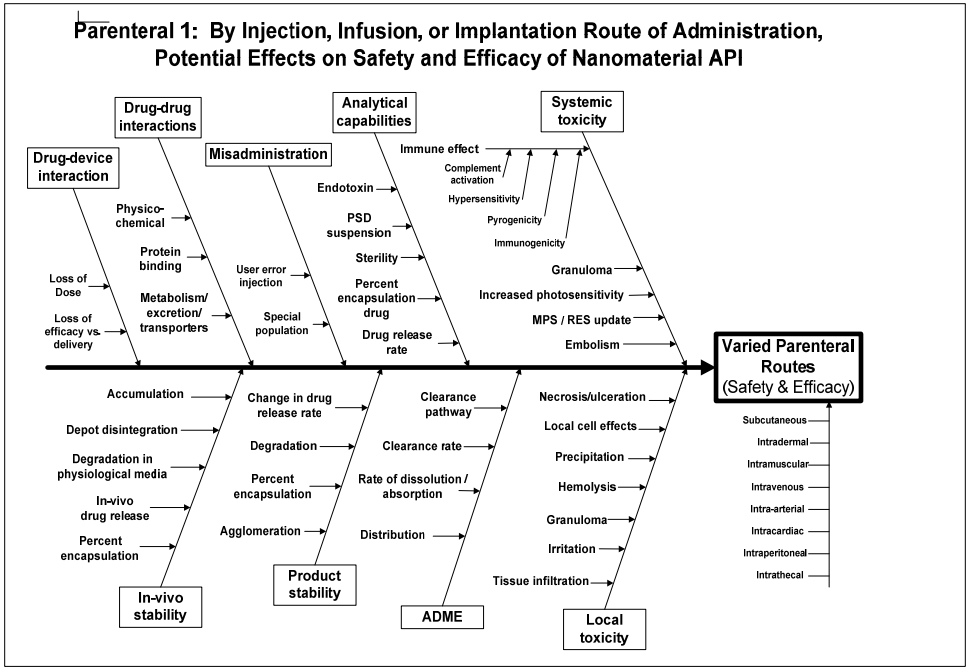


Identification of Potential Risk Factors to SQE from Nanomaterial API

Parenteral Route of Administration

Various Parenteral Routes of Administration

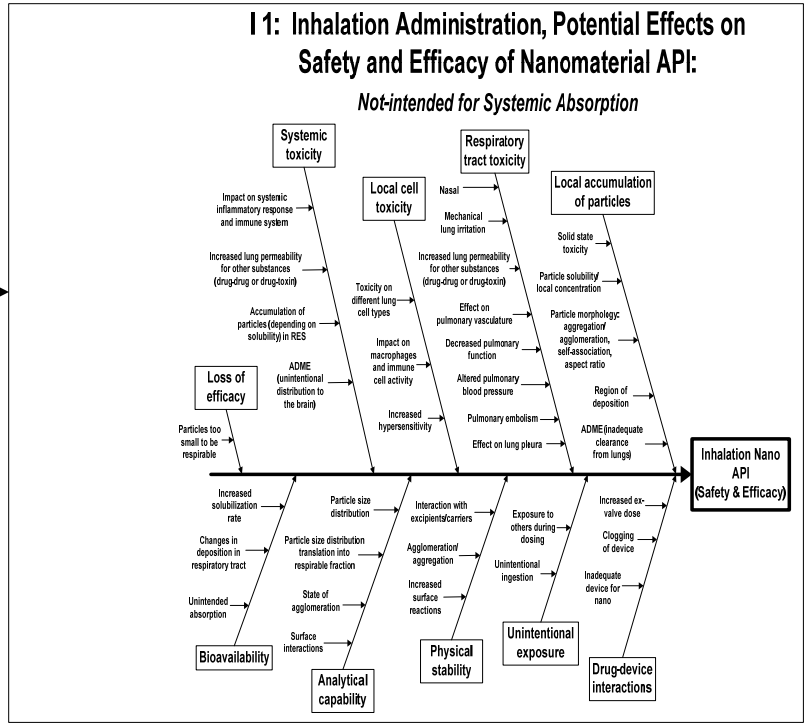
- Subcutaneous
- Intradermal
- Intramuscular
- Intraveneous
- Intra-arterial
- Intracardiac
- Intraperitoneal
- Intrathecal



Identification of Potential Risk Factors to SQE from Nanomaterial API

Inhalation Route of Administration

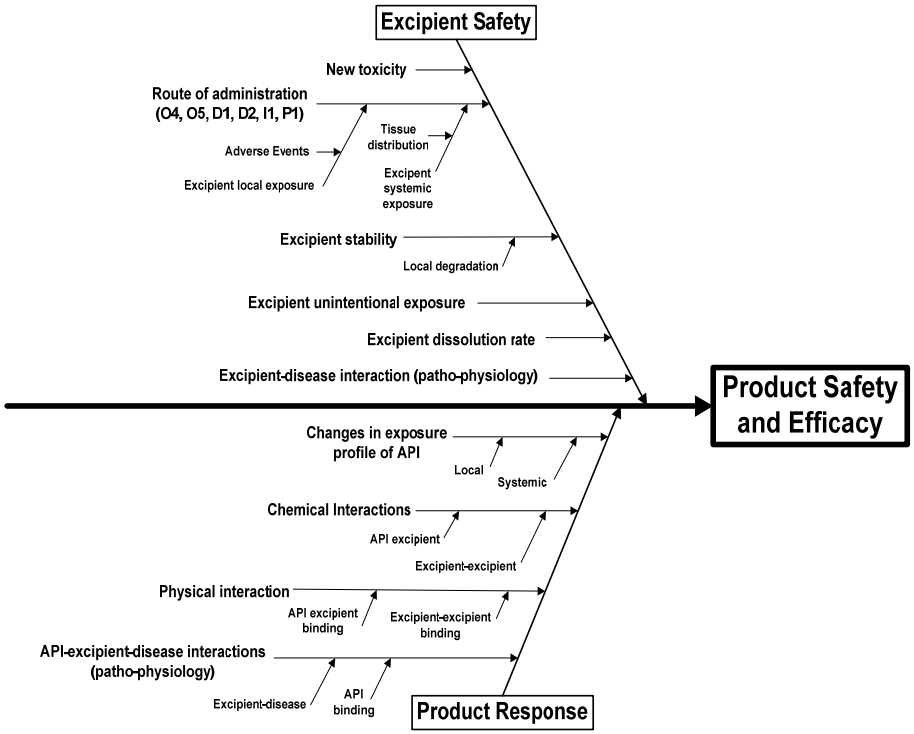
Inhalation Products



Identification of Potential Risk Factors to SQE from Nanomaterial

Excipients - all routes of administration

E1: Potential Effects on Safety and Efficacy of Drug Products Containing Nanomaterial Excipients -- *all routes of administration*



Systematic Approach

1. Ishikawa Diagram

- Tool used to identify the potential risk factors and map them by category
- These are factors that may lead to an effect on safety and/or efficacy, if drug product component is a nanomaterial

2. Gap Analysis

- Identify any areas for improvement in our current approaches (e.g., policy, review procedure, or data requirements)
- Document whether current approaches can evaluate the potential risk or whether additional work is necessary
- Develop recommendations

Gap Analysis

1. Risk areas identified by Ishikawa diagrams are transferred to a worksheet.

2. Current practices that would address the risk are reviewed.

3. Areas for improvement in the current practices, if any, are noted.

4. Proposed improvements are listed.

Risk Management Table

Oral Route of Administration

Risk Identified: Risk Factor Category	**Sub Risk Factor, Primary and/or Secondary Cause**	**What do we do or require currently to address this risk?** *Guidelines, Policies, Submitted Data, or Research that currently address this risk*	**Is this sufficient to address nanomaterial API effects and/or causes?** *Identified Area for Improvement*	**Potential approach to gap, e.g. proposed solution, references to future or proposed work, if any.** *Area of Focus*
Analytical Methods	Dissolution/Release Rate Method	Evaluate dissolution/release rate method development report for discrimination and justification of parameters. Evaluate method against changes in formulation or IV/IVR Methods are reviewed following the same requirements for discrimination, development information, etc, regardless of Case A, B, C, or D. For OTC, methods are compendial and evaluation is done against compendial methods. BE data would also catch differences in modified release formulations and could trigger more work on method development information.	For IR, BE studies may need to take into consideration API PSD impact on dissolution for BCS Class II and BCS Class IV. Monographs methods may or may not be suitable for reformulated materials if change to nano API has occurred. Any in-vitro methods that use filtration and are being used for comparative evaluation of quality may need to be evaluated further. The review of any unconventional methodology.	Reminder that for nanomaterials to focus on understanding the effect of particle size distribution on bioavailability and dissolution for Immediate Release, particularly for BCS II and IV, where API PSD may have impact on dissolution Request studies to show API PSD impact on dissolution, a dissolution specification is requested that covers ranges in dissolution may need to show in vivo data (“clinically relevant specs”). Conventional methodology involving filtration of materials in in-vitro analytical methods (e.g. Dissolution, Assay) may need to be revaluated when applied to nano materials.

Risk Management Results – Oral

Areas for Improvement

- **Analytical Methods**
  - Traditional methods may not be able to adequately identify/characterize nanomaterials
    - Physical testing
    - *In vitro* dissolution filtration issues
  - Awareness and further research
- **Product Performance**
  - Change in particle size can affect product performance.
  - Understanding effect of particle size on bioavailability/dissolution
    - Especially important for low solubility drugs
- **Safety**
  - Unintended exposure
  - Clarification needed on requirements for
    - Studies when formulation change to nanomaterial API
    - Impact of API particle size change when no absorption is intended

Risk Management Results – Dermal

Areas for Improvement

- **Analytical Methods**
  - Traditional methods may not be able to adequately identify/characterize nanomaterial
    - Physical testing
    - *In vitro* release tests for nanomaterial drugs
  - Awareness and further research
- **Product Performance**
  - Change in particle size can affect product performance
  - Effect of particle size change on degradation (photostability)
- **Safety**
  - Clarification on studies needed for a change to nanomaterial API
    - Safety studies not typically conducted in absence of formulation change
  - Product development considerations
    - Determine if change to nanomaterial API affects skin penetration and systemic exposure
    - Determine effects and occurrence of second hand exposure

Risk Management Results – Inhalation

Areas for Improvement

- **Analytical Methods**
  - Traditional methods may not be able to adequately identify/characterize nanomaterial
    - Update techniques for aerosols and other inhaled formulations
      - Particle size distribution
      - Alternatives to the cascade impactor
- **Product performance** is sensitive to particle size change
- **Safety**
  - Unintended exposure
  - Clarification on studies needed for a change to nanomaterial API
  - Product development considerations
    - Determine if change to nanomaterial API affects distribution within the respiratory tract, accumulation, and systemic exposure
    - Determine effects and occurrence of second hand exposure

Risk Management Results – Parenteral (suspensions)

Areas for Improvement

- **Analytical Method**
  - Traditional methods may not be able to adequately identify/characterize nanomaterial
    - Additional evaluation of the effect of particle size changes
    - Impact on stability
- **Product performance** is sensitive to particle size change
- **Safety**
  - Safety evaluation of generics with nanomaterial API when Reference Listed Drug is not
  - Verification of physical compatibility *in vitro* with co-administered drugs
  - Inability to visually differentiate nanomaterial parenteral suspensions from solutions

Risk Management Results – Excipients

Areas for Improvement

- Similar to those associated with nanomaterial API per route of administration
  - Particle size change does not routinely trigger safety evaluation for excipients
  - Particle size data of excipients is not routinely provided in applications
  - Consider requesting data on the effects of particle size changes in excipients
  - Current excipient non-clinical guidance may need to be updated to address particle size changes in excipients
  - Increase awareness regarding the effects of excipient particle size changes

Risk Management Results
Potential Areas for Future Focus

Understanding impact of particle size changes on:

- Manufacturing control strategy
  - Capability of analytical methods to characterize nanomaterials
  - Potential effects of nanomaterial on process parameters
- Safety
  - Toxicity
  - Biodistribution
- Efficacy
  - *In vitro* performance of formulation for particle size changes
  - Bioequivalence

Conclusions

- Risk management exercise
  - Potential risks to safety, quality and efficacy have been identified
  - Current review practices are adequate
    - Particularly when the nanomaterial API is studied in the product from early development
    - Potential issues if change occurs after Phase III clinical trials
  - Identified potential areas for improvement
    - Analytical methods
    - Clarification of safety evaluation needs
    - Bioequivalency and dissolution testing
    - CDER reviewers training
    - Research may be needed

Work Group Next Steps

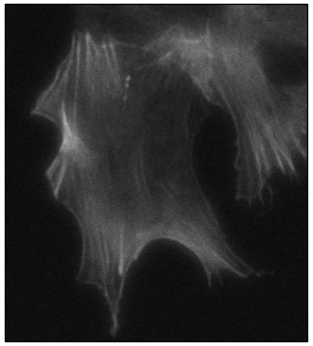
1. Publish article on the risk management process
2. Hold public workshop
3. Potential draft guidance document and/or reviewer guide/MaPP

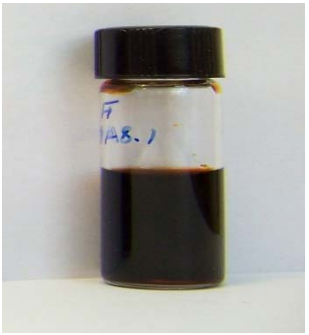
Nanotechnology Research at CDER/OTR

Katherine M. Tyner, Ph.D.
Office of Testing and Research
Division of Drug Safety Research
August 9, 2012

Agenda

- Introduction to OTR's Nanotechnology Regulatory Research
- Examples of OTR's Nanotechnology Regulatory Research
- Regulatory Research on Nano-Sunscreens
- Future Perspectives & Summary





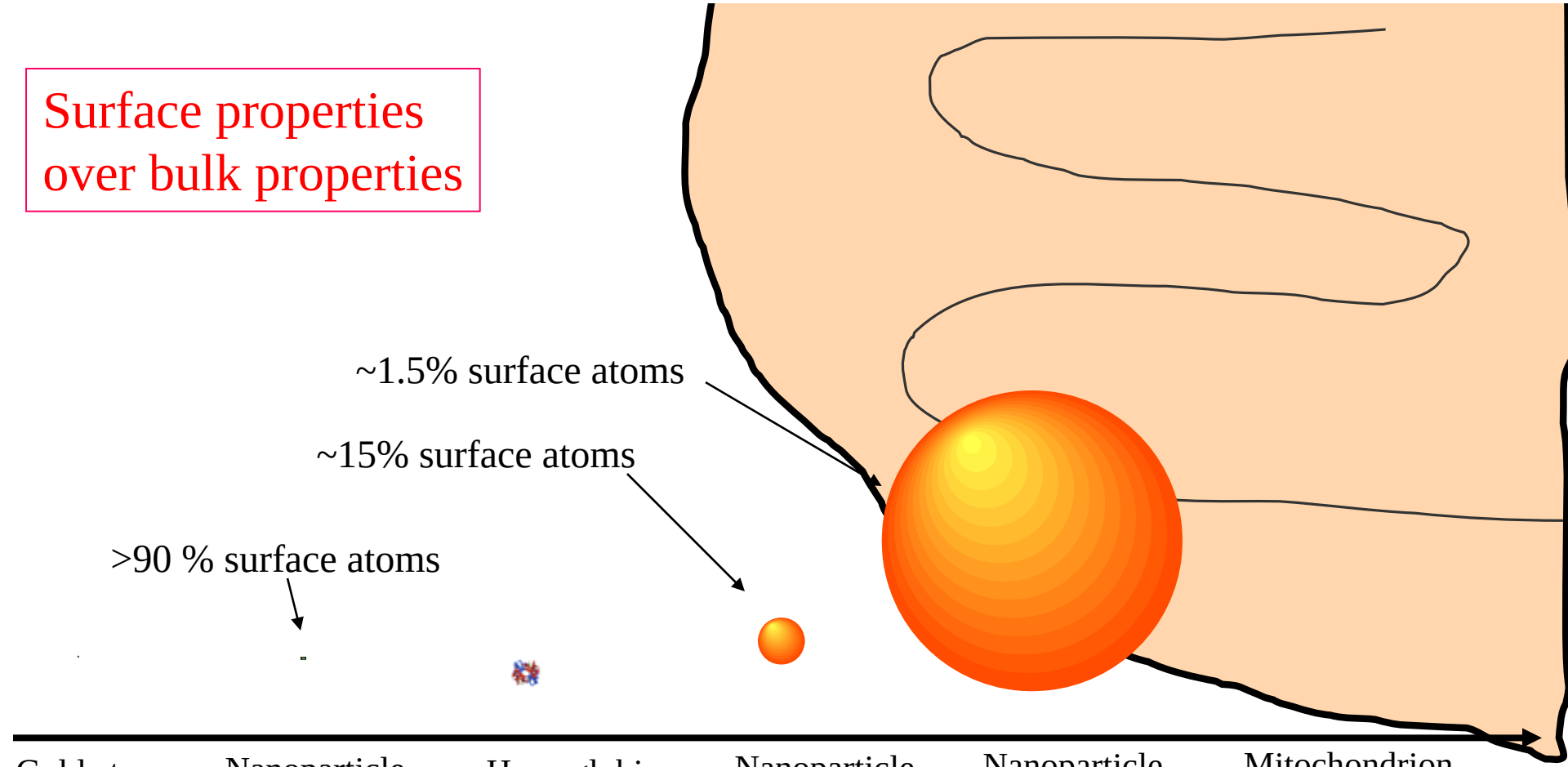
Introduction to OTR's Nanotechnology Regulatory Research

Office of Testing and Research (OTR)
Dr. Vince Vilker, Director

- Division of Drug Safety Research (DDSR)
  - Dr. Tom Colatsky—Division Director
- Division of Pharmaceutical Analysis (DPA)
  - Dr. Cindy Buhse—Division Director
- Division of Product Quality Research (DPQR)
  - Dr. Mansoor Khan—Division Director

The Scale of Nanotechnology

Surface properties over bulk properties



Gold atom	Nanoparticle	Hemoglobin	Nanoparticle	Nanoparticle	Mitochondrion
0.1 nm	1 nm	6 nm	10 nm	100 nm	1000+ nm
	Oligonucleotides		**Antibodies**	**Viruses**	

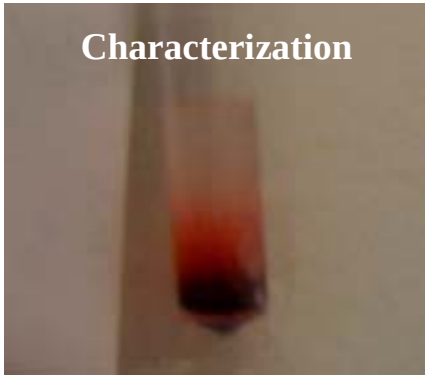
Why Apply Nanotechnology to Products?

Combination of size and surface effects → novel properties

- Different properties than corresponding small molecule & bulk material
  - Distribution – Example: Liposomes
  - Bioavailability – Example: Nanocrystals
- Enhancement of API
  - More surface reactions – Example: Nano-sunscreens
  - Stabilization of API – Example: Micelles
- Multi-functional capabilities
  - Targeted delivery
  - Imaging plus drug delivery

CDER/OTR Nanotechnology Regulatory Research Focus

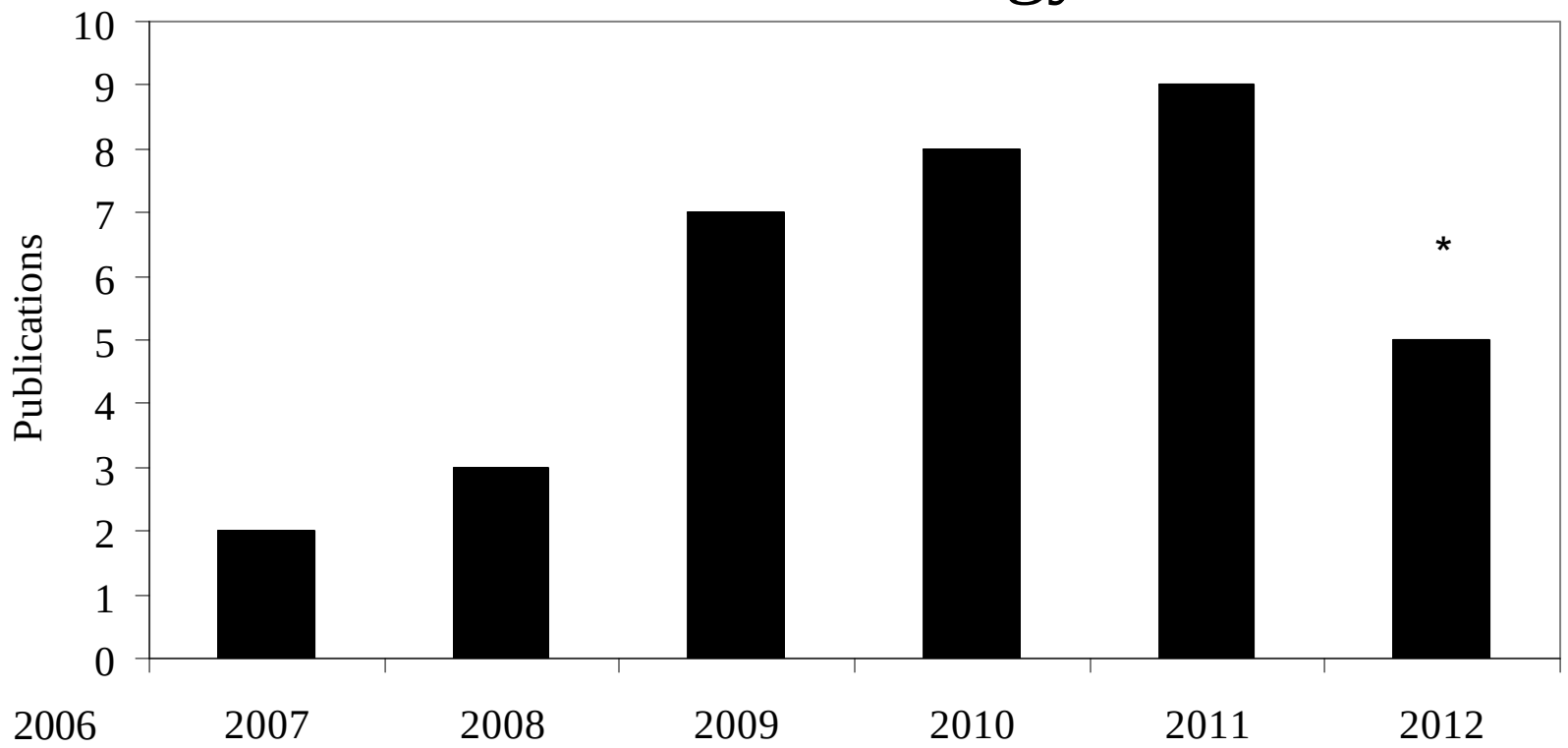
- Assessing the adequacy of current methods in assessing the quality, efficacy, and safety of therapeutics containing nanomaterials
- Determine the relationship between the physicochemical properties of nanomaterials and their biological effects
- Determine the mechanism of interaction between nanomaterials and the body at the molecular, cellular, and tissue level
- Assist in reviewer training in understanding the regulatory issues associated with therapeutics containing nanomaterials



CDER/OTR Regulatory Research Deliverables

- Generating real time data for reviewer use
- Participating in seminars/trainings/courses
- Providing expert consults
- Developing external/internal resources

CDER/OTR Nanotechnology Publications

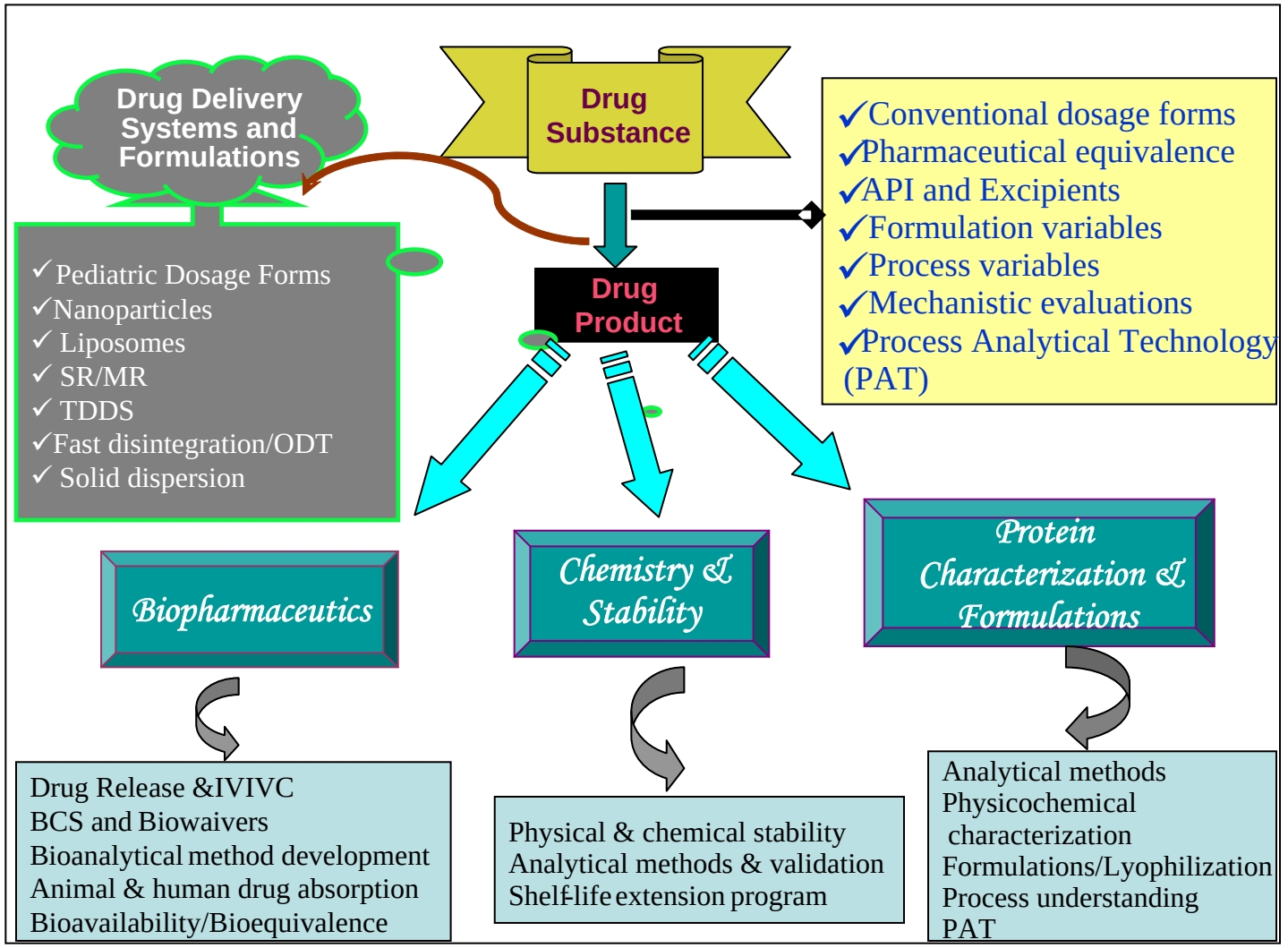


- Formation of FDA Nanotechnology Task Force
- Task Force Report Issued
- Nanotechnology public meeting
- CDER nanotechnology MaPP issued
- FDA draft guidance on nanotechnology issued
- CDER establishes risk assessment working group

Examples of OTR's Nanotechnology Regulatory Research

Division of Product Quality Research

Dr. Mansoor Khan, Director



Thermodynamic Stability of Sodium Ferric Gluconate Nanoformulations

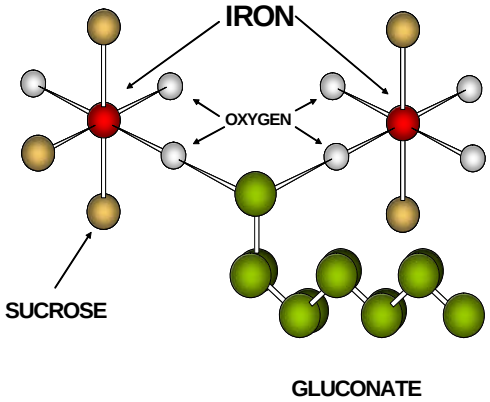
Purpose: To evaluate and classify some nano drug products as thermodynamically or kinetically stable

I. Thermodynamic Stability Study

- *Stress Testing Temperature (short term)*
- *Stress Testing Temperature (long term)*
- *Excipient Dilution Testing*
- *pH Testing*

II. Characterization Study

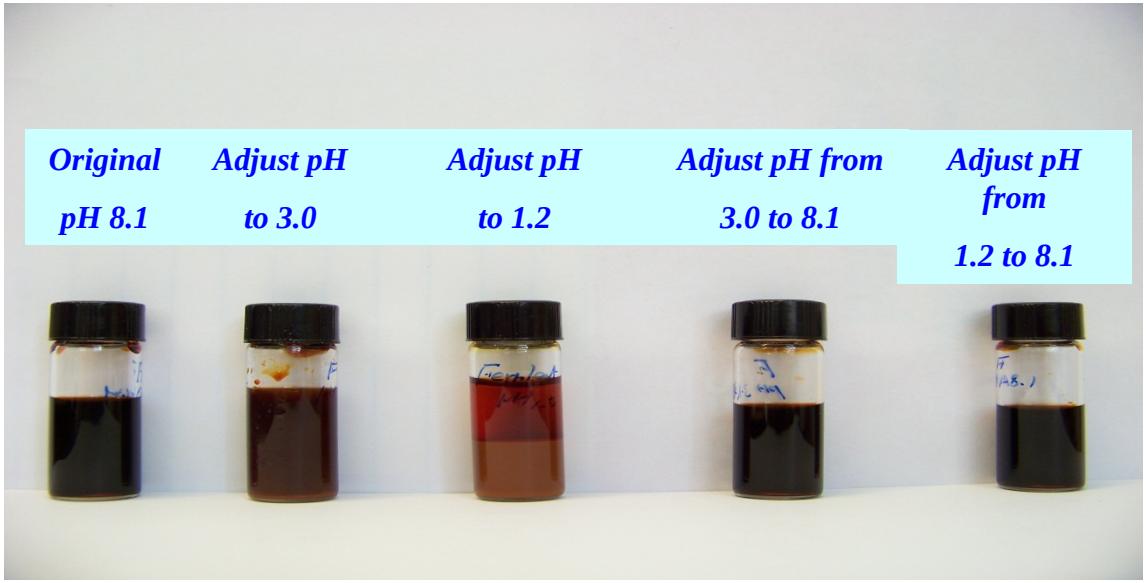
- *Dialysis*
- *Electrolyte Testing*
- *Osmolality*
- *Particle Size*
- *Turbidity*
- *Zeta Potential*



Quality Attribute: Molecular Weight (MW) by Gel Permeation Chromatography

Participants: Yongshen Yang, Rakhi Shah, Patrick Faustino, Andre Raw, Lawrence Yu, Mansoor Khan

Thermodynamic Stability of Sodium Ferric Gluconate Nanoformulations



Original pH (8.1)	Adjust pH to 3.0	Adjust pH to 1.2	Adjust pH from 3.0 back to 8.1	Adjust pH from 1.2 back to 8.1
377800 ± 2900	375500 ± 600	No peak	371800 ± 1000	365200 ± 500

- The MW as determined by HP-GPC was used as the quality attribute to determine the stability of the formulation under different stress conditions.

- These studies allowed the Office of Generic Drugs to approve a generic colloidal iron nano product

Yang et al., J. Pharm. Sci, 99(1):142-53, 2010.

Division of Drug Safety Research

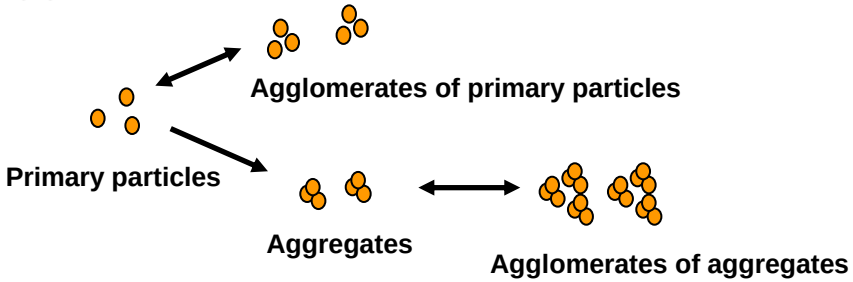
Dr. Tom Colatsky, Director

- Further the understanding of methods used to detect and characterize nanomaterials in CDER-regulated products.

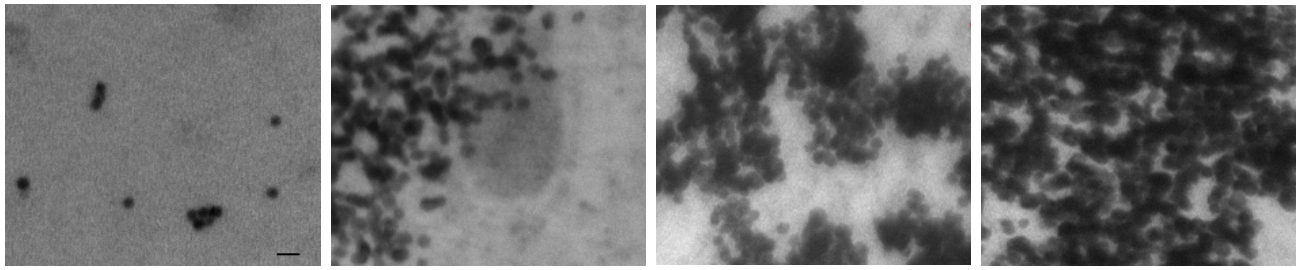
- Understand how the physico-chemical properties of nanomaterials contribute to toxicity and/or unanticipated biological effects

Self-associated AuNP Structures and Biodistribution

- Aggregation/agglomeration is a common issue with nanoparticle suspensions



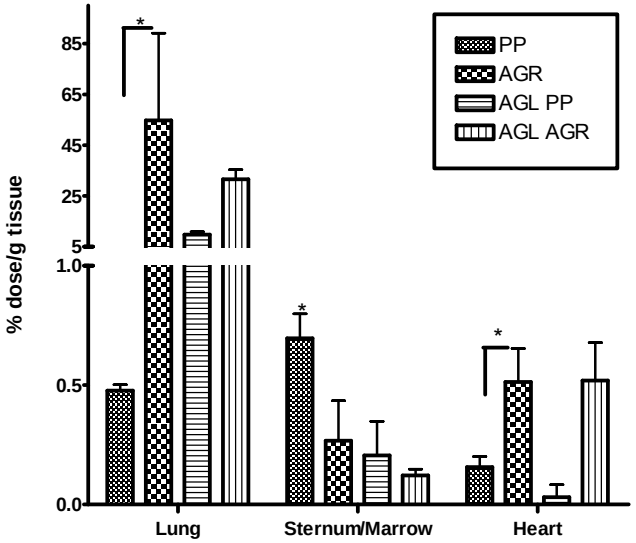
- Questions addressed:
  - Could agglomeration/aggregation be missed during small molecule stability testing?
  - Will the unanticipated administration of nanoparticle superstructures be a safety risk?
    - Biodistribution/Toxicity

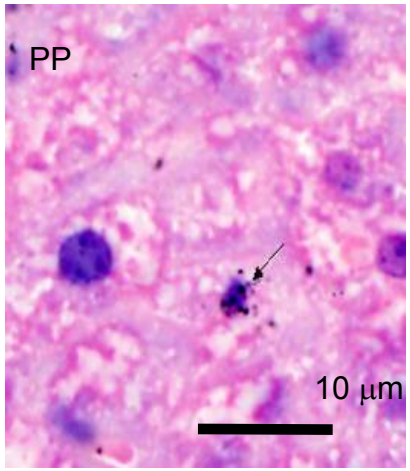


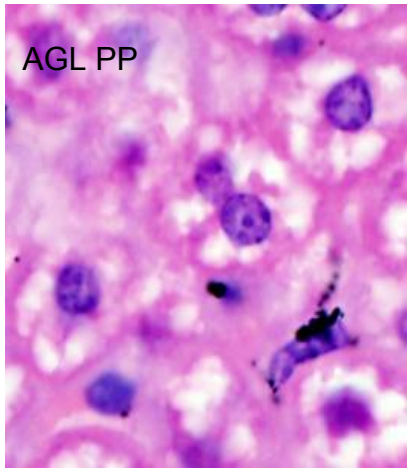
- Participants
  - Athena Keene, David Peters, Rodney Rouse, Sharron Stewart, Elliot Rosen, Katherine Tyner

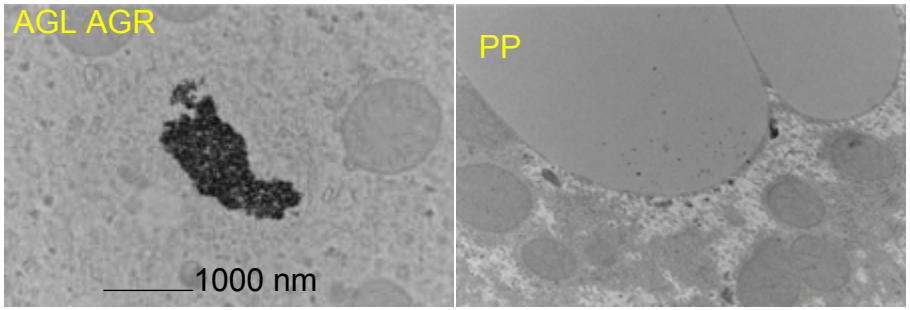
Keene, A.M. et al.,Tissue and cellular distribution of gold nanoparticles varies based on aggregation/agglomeration status. *Nanomedicine.*7(2) 199-209, 2012.

Self-Associated NP Structures and Biodistribution









- Structures have different biodistribution
- Tissue, cellular and sub-cellular locations
- Potential for different toxicity pathways

Keene, A.M. et al.,Tissue and cellular distribution of gold nanoparticles varies based on aggregation/agglomeration status. *Nanomedicine.*7(2) 199-209, 2012.

Regulatory Research on Nano-Sunscreens

CDER's Drivers for Nano-Sunscreen Research

- Sunscreens containing titanium dioxide (TiO_2) and/or zinc oxide (ZnO) nanoparticles
  - Emergence of products was reflected in an industry shift from micron-size (pigment grade) to nano-size particles
    - Cosmetic, performance, and cost

- Public and Agency interest in the safety and efficacy of these products

- Multiple CDER research projects were designed to address CMC, safety, and efficacy questions on nano-sunscreens

Methodology for Detection/Characterization of Nano TiO_2/ZnO

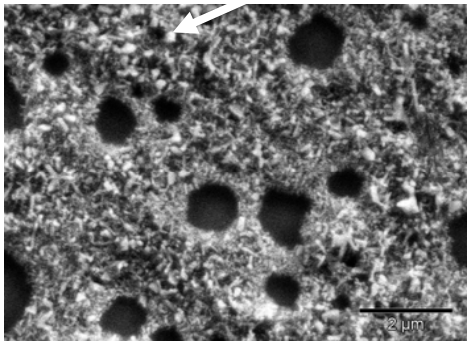
- Questions addressed:
  - Do commercial sunscreens contain nanoparticles?
  - What methods are available for detection/characterization
  - What attributes impact safety/efficacy?

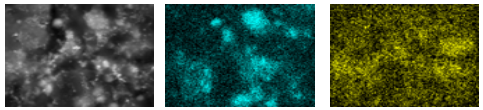
• Size: primary particle (PP), aggregate		Transparency/SPF
• Particle size distribution		Broad spectrum coverage
• Agglomeration (AGL) state	→	Skin coverage
• Particle dispersion (3D)		Applicability
• Particle composition		SPF/broad spectrum
• Surface composition		Surface reactions

- Publications:
  - Tyner, K.M. et al., *Nanomedicine*, **4**(2) 145-159 (2009).
- Participants:
  - Katherine Tyner, Anna Wokovich, Bill Doub, Cindy Buhse, Li-Piing Sung (NIST), Stephanie Watson (NIST), Nakissa Sadrieh

Methodology for Detection/Characterization of Nano TiO_2/ZnO

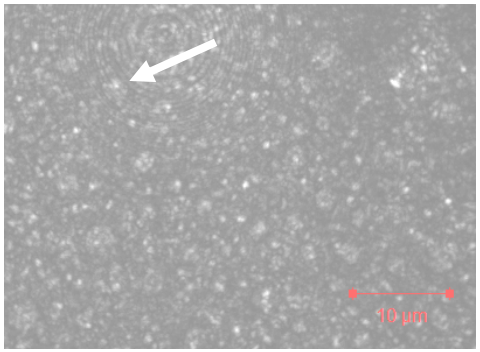
Variable pressure scanning electron microscopy



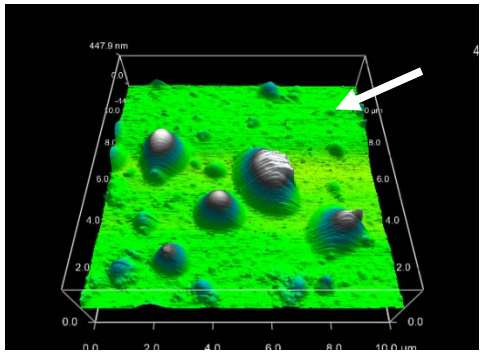


SEM Ti Zn

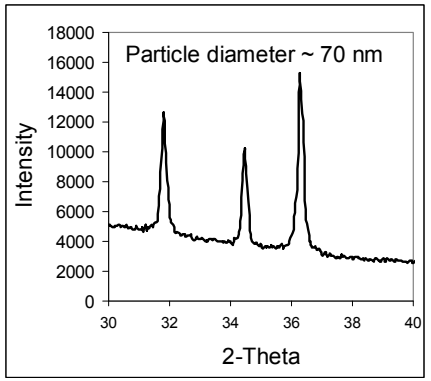
Laser scanning confocal microscopy



Atomic force microscopy



X-ray diffraction



- Multiple techniques provide complementary information
  - Detection/characterization should use at least two methods
- Commercial sunscreens may contain nanoparticles
  - ZnO and TiO_2
  - In the form of primary particles and/or aggregates & agglomerates

Formulation and Evaluation of Sunscreens Formulated With Various Forms and Sizes of TiO_2

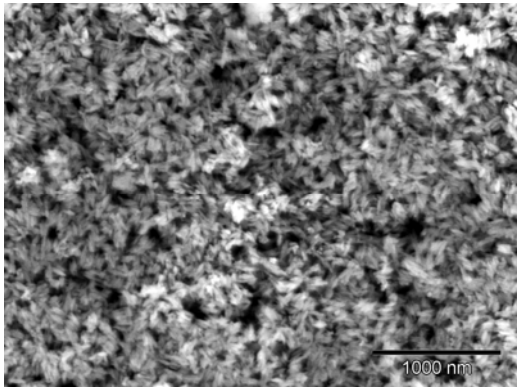
- Questions addressed:
  - Does the formulation process cause a change in the size or morphology of TiO_2 NPs?
    - Uncoated nano-TiO_2
    - Coated nano-TiO_2
    - Sub-micron TiO_2
    - Blank sunscreen
  - Sunscreen formulations used for subsequent dermal penetration studies/permeability enhancement studies
- Publications:
  - Wokovich, A.M. et al., *Drug Development and Industrial Pharmacy*. **35**(10) 1180-1189 (2009).
  - Sadrieh N. et al., *Toxicological Sciences* **115** (1) 156–166 (2010).
- Participants:
  - Anna Wokovich, Katherine Tyner, Bill Doub, Nakissa Sadrieh, Cindy Buhse

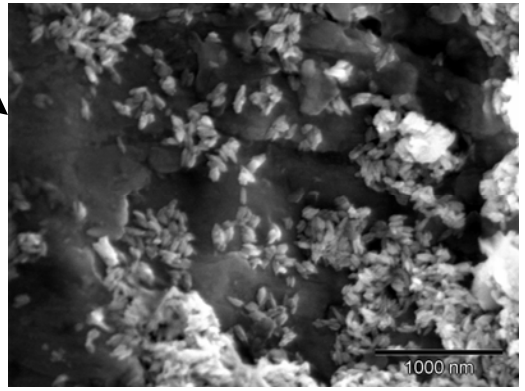
Formulation and Evaluation of Sunscreens Formulated With Various Forms and Sizes of TiO_2

TABLE 3

Particle sizing results of titanium dioxide raw materials and formulations containing titanium dioxide

Sample	Particle Size by SEM	Particle size from XRD line-broadening calculations
uncoated nano TiO_2	30 nm - 50 nm	26 nm
uncoated nano TiO_2 formulation	30 nm - 50 nm	30 nm
coated nano TiO_2	20 nm - 30 nm in diameter and about 50 nm - 150 nm in length	19 nm
coated nano TiO_2 formulation	20 nm - 30 nm in diameter and about 50 nm - 150 nm in length	24 nm
sub-micron TiO_2	300 nm - 500 nm	could not be determined
sub-micron TiO_2 formulation	300 nm - 500 nm	could not be determined





- The formulation process did not affect the size or shape of the TiO_2 nanoparticles

Wokovich, A.M. et al., *Drug Development and Industrial Pharmacy*. **35**(10) 1180-1189 (2009).

Determining the Effects of Agglomeration/Aggregation on Sunscreen Efficacy

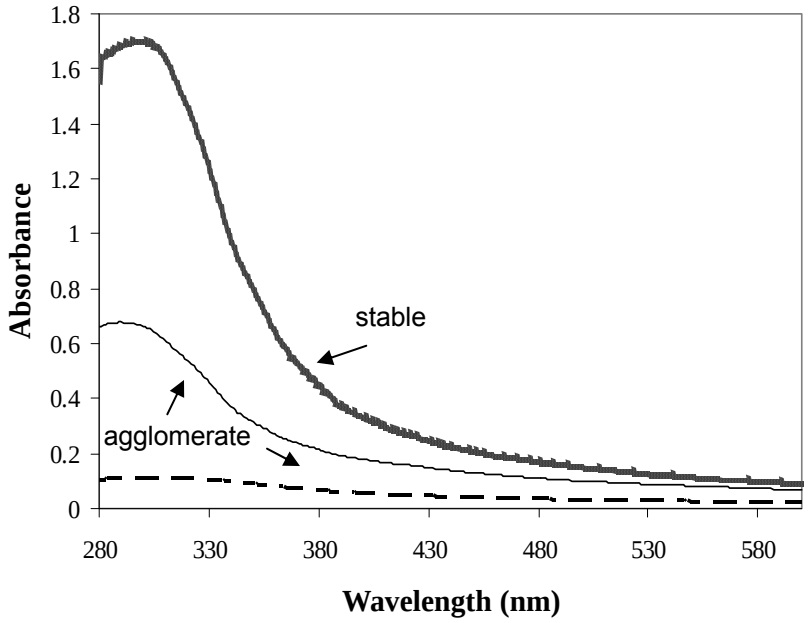
- Claims that TiO_2 and ZnO nanoparticles agglomerate into micro-sized features and no longer function as nanoparticles.
  - Is this a valid claim?

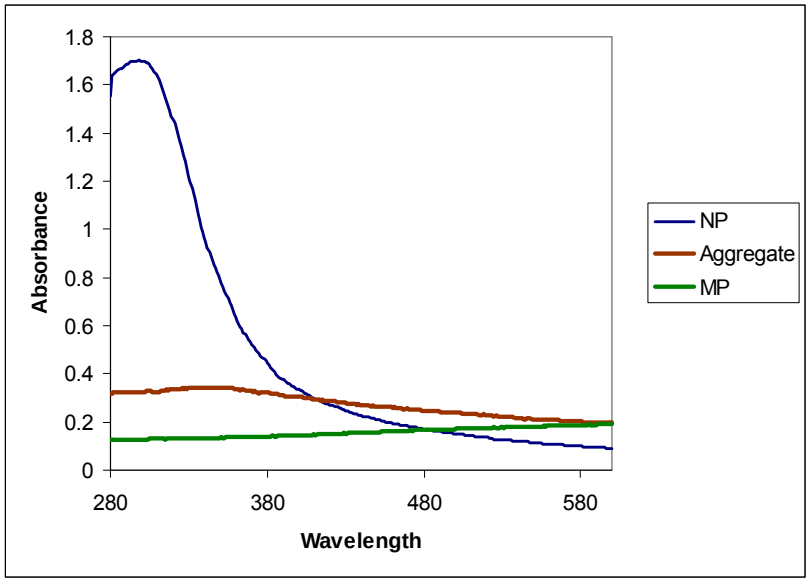
- Questions addressed:
  - Do NPs behave differently from macroscale materials?
  - Does the state of the NP matter for safety/efficacy?

- Publications:
  - Tyner, K.M. et al., *International Journal of Cosmetic Science.* **33** 234-244 (2011)

- Participants:
  - Katherine Tyner, Anna Wokovich, Dianne Godar (CDRH), Bill Doub, Nakissa Sadrieh

Determining the Effects of Agglomeration/Aggregation on Sunscreen Efficacy





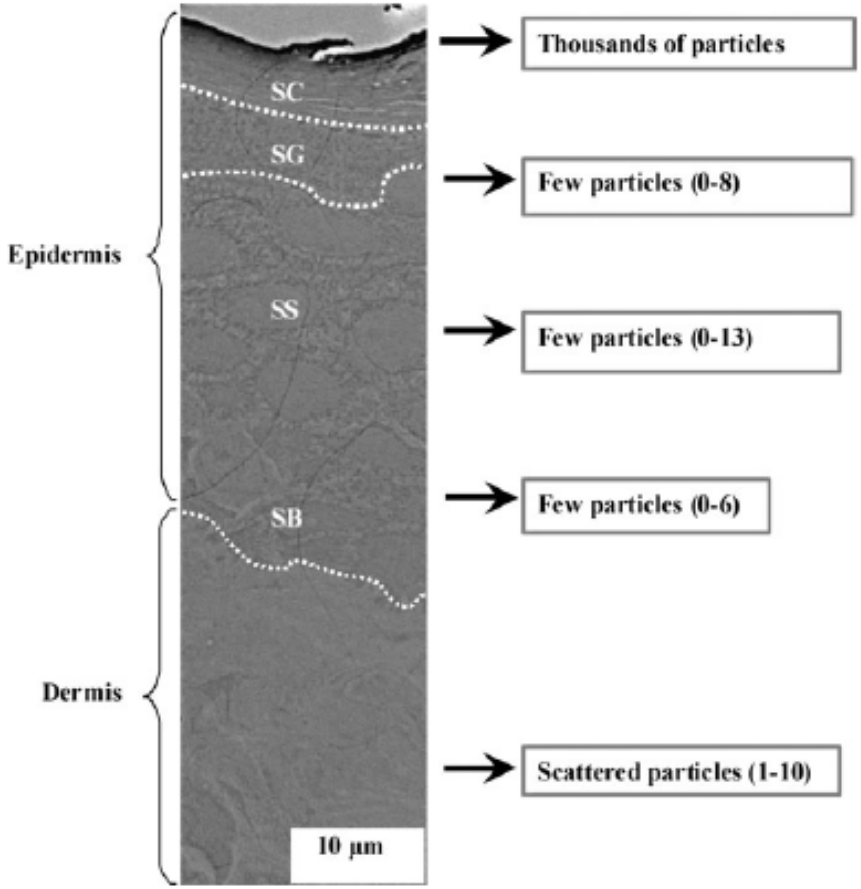
- Agglomeration and aggregation of TiO_2 reduces the amount of UV attenuation
  - Both reductions most likely stem from a reduction in functional surface area
- Agglomerated and aggregated nano-TiO_2 absorbed more UV light than the corresponding micron-size TiO_2
  - Functional surface area

Dermal Penetration of Nano TiO_2 Formulated into Sunscreens

- Question addressed:
  - Do TiO_2 NPs formulated into sunscreens penetrate the skin?
- Key question surrounding nano-sunscreen safety
  - Mini-pigs as dermal model.
    - Three sunscreens (+ control) formulated with different forms and sizes of TiO_2
- Publications:
  - Sadrieh, N. et al., *Toxicological Sciences* **115** (1) 156–166 (2010).
- Participants:
  - CDER: Nakissa Sadrieh, Anna Wokovich, Neera Gopee, Bill Doub, Cindy Buhse
  - CDRH: Sharon Miller, Anant Agrawal, Janusz Beer, Harry Bushar, Ilko Ilev, Barbara Zmudzka
  - NCTR: Paul Siitonen, Christy Cozart, Paul Howard
  - NCI & NCL: Jiwen Zheng, David Parmiter, Anil Patri, Scott McNeil, Michaela Brenner, Sergio Coelho, Diana Haines, Jennifer Hall, Vincent Hearing, Kunio Nagashima,
  - OC: Boris Lushniak
  - NIEHS: Cynthia Smith, Nigel Walker
  - Unaffiliated: Lynn Herman, Katalin Korossy

Dermal Penetration of Nano TiO_2 Formulated into Sunscreens

- Pig skin
  - Lack of significant dermal penetration of titanium dioxide from sunscreen formulations containing nano- and submicron-size TiO_2 particles.
  - Other studies show similar results this for TiO_2 and ZnO-based sunscreens

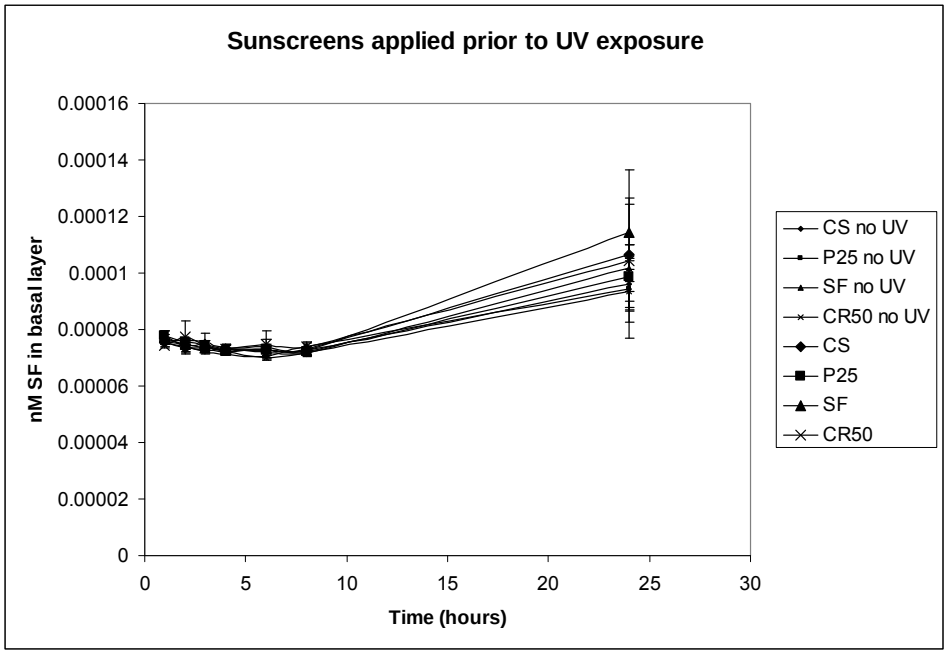


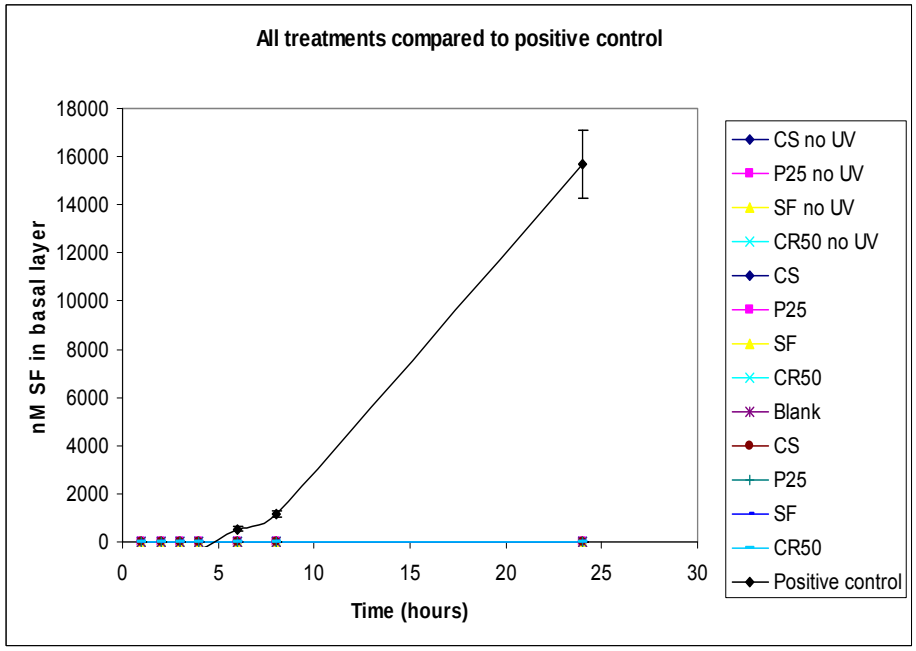
Sadrieh et al., Toxicological Sciences, 115(1), 156-166 (2010)

Evaluating TiO_2 NPs as Permeability Enhancers

- Question addressed:
  - Do NPs act as permeability enhancers for the skin?
- *In vitro* skin models
  - Unmodified
  - During UV exposure (to produce a sunburn on unprotected skin)
  - After UV exposure (sunburn)
- Publications:
  - Tyner, K.M. et al., *International Journal of Cosmetic Science.* **33** 234-244 (2011)
- Participants:
  - Katherine Tyner, Anna Wokovich, Dianne Godar (CDRH), Bill Doub, Nakissa Sadrieh

Evaluating TiO_2 NPs as Permeability Enhancers





- No enhanced permeability
  - No UV exposure
  - During sunscreen exposure (sunscreen function)
  - After UV exposure (application of sunscreen after sunburn)

Tyner, K.M. et al., *International Journal of Cosmetic Science.* **33** 234-244 (2011)

Overall Impact

- Addressed specific questions concerning the safety and efficacy of nano-sunscreens
- Resulted in specific methodology development & in house expertise
- Research results produced specific advice to review divisions and sponsors

Future Perspectives & Summary

Summary

- Nanotechnology has great potential to impact medical research and drug discovery

- CDER/OTR is conducting regulatory research that addresses key questions concerning nanotechnology applied to drug products
  - Formulation and characterization
  - Nanomaterial physicochemical properties & biological effects
  - Mechanism of interaction between nanomaterials and the body

- Future work will continue to focus on current issues as identified by the FDA Nanotechnology Task Force, risk assessment exercises, & current state of knowledge
  - Contribute to potential CDER guidances and MaPPs on nanotechnology

Acknowledgements

- Office of Pharmaceutical Science (OPS)
  - Nakisssa Sadrieh—Associate Director for Research Policy Implementation
- Office of Testing and Research (OTR)
  - Immediate Office (IO)
    - Dr. Vince Vilker, PhD—Office Director
    - Dr. Joe Hanig, PhD—Associate Director for Resarch
  - Division of Drug Safety Research (DDSR)
    - Dr. Tom Colatsky, PhD –Division Director
  - Division of Pharmaceutical Analysis (DPA)
    - Dr. Cindy Buhse—Division Director
  - Division of Product Quality Research (DPQR)
    - Dr. Mansoor Khan—Division Director
- Non-base Competitive Grant Funding
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  - Regulatory Science and Review Enhancement (RSR) intramural funding